FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

NASACORT® AQ Nasal Spray

Aqueous suspension of triamcinolone acetonide, 55 mcg/spray

NDA 20-468

Nonprescription Drugs Advisory Committee

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ABBREVIATIONS

ACTH:	adrenocorticotropic hormone
AE:	adverse event
AERS:	Adverse Event Reporting System
AESI:	adverse events of special interest
AQ:	aqueous
AR:	allergic rhinitis
AUC:	area-under-the-curve
BID:	two times a day
CFC:	chlorofluorocarbon
CI:	confidence interval
CIL:	Consumer Information Leaflet
C_{max}:	maximum concentration
DFL:	Drug Facts Label
DKA:	diabetic ketoacidosis
FDA:	Food and Drug Administration
HCP:	healthcare professional
HLT:	high level term
HPA:	hypothalamic pituitary adrenal
IgE:	immunoglobulin E
IMS:	Intercontinental Medical Statistics
INS:	intranasal steroid
ITT:	intent-to-treat
LS:	least squares
mcg:	microgram
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intent-to-treat
NDA:	New Drug Application
NEC:	not elsewhere classified
NI:	nasal index score
NRQLQ:	Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire
OAH:	oral antihistamines
OTC:	over-the-counter
PAR:	perennial allergic rhinitis
PK:	pharmacokinetics
PP:	per protocol
PSQI:	Pittsburgh sleep quality index
PT:	preferred term
QID:	four times a day
QoL:	quality of life
REALM:	rapid estimate of adult literacy in medicine
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire
Rx:	prescription
SAE:	serious adverse event
SAR:	seasonal allergic rhinitis
SE:	standard error

SMQ:	standardized MedDRA queries
sNDA:	supplemental New Drug Application
SOC:	system organ class
$t_{1/2}$:	half-life
TAA:	triamcinolone acetonide
TEAE:	treatment emergent adverse event
TNSS:	total nasal symptom score
USPI:	US prescribing information
WHO:	World Health Organization

1 EXECUTIVE SUMMARY

Nasacort® AQ Nasal Spray is an aqueous suspension of triamcinolone acetonide (TAA) [Nasacort AQ or TAA-AQ will be used interchangeably in this briefing document]. Sanofi-aventis U.S. LLC and Chattem Inc., each A SANOFI COMPANY collectively referred to as Sanofi, submitted an application to the FDA with data supporting a switch of Nasacort AQ from prescription to over-the-counter (OTC) status.

Nasacort AQ is currently approved as a prescription product for intranasal administration to treat nasal symptoms of seasonal and perennial allergic rhinitis (AR). AR may present with seasonal or perennial symptoms or a mixture of the two. Nasacort AQ was approved in the United States in 1996 for use in adults and adolescents 12 years of age and older. In 1997, the indication was extended to children 6 through 11 years of age and in 2008, the indication was extended to children 2 through 5 years of age.

Each actuation of the metered dose pump delivers 55 mcg of TAA per spray. The recommended dosing by age is as follows:

- In adults and adolescents (≥ 12 years), the starting and maximum dose is two sprays in each nostril once daily (220 mcg/day). When symptoms are controlled, the dose may be reduced to one spray in each nostril once daily (110 mcg/day).

- For children 6 through 11 years of age, the starting dose is one spray in each nostril once daily (110 mcg/day) with a maximum of two sprays in each nostril once daily (220 mcg/day).

- For children 2 through 5 years of age, the starting and maximum dose is one spray in each nostril once daily (110 mcg/day).

The proposed OTC indication is for temporary relief of hay fever or other upper respiratory allergies (nasal congestion, runny nose, sneezing, and itchy nose) in children 2 years of age and older, adolescents and adults. The proposed OTC product is the same formulation and spray pump with the same dosing instructions as the currently approved Nasacort AQ.

While Nasacort AQ would be the first intranasal steroid (INS) approved for the OTC setting in the US, AR is a well-established OTC indication and consumers are able to self-recognize and self-treat AR with many OTC products. A unique aspect of consumer use of the Nasacort AQ nasal spray in the OTC setting is consumer operation of the pump without health care professional (HCP) involvement. Following the FDA's recommendations, Sanofi conducted label comprehension and human factors studies designed to evaluate consumer understanding and actual operation of the spray pump as described in the Drug Facts Label (DFL) and Consumer Information Leaflet (CIL). Sanofi also evaluated consumer comprehension of label directions and warnings.

A key consideration in the OTC switch approval of Nasacort AQ is the age recommendation for OTC labeling. In evaluating the appropriateness of Nasacort AQ for OTC use, including down to the age of 2 years, Sanofi conducted a comprehensive review of Nasacort AQ safety

information. The findings from this review are provided in Section 4 of the briefing book. Sanofi also discussed with the FDA the appropriate age recommendation for the OTC labeling. Based on the comprehensive safety review of Nasacort AQ and consistent with the FDA's recommendation, Sanofi filed for a full switch (2 years of age and older) where the indication, population and duration of use reflect the current approved prescription labeling.

This briefing book reviews the findings from the label comprehension and human factors studies, the efficacy and safety observed in the initial and supplemental NDAs and the experience reported in post-marketing. The proposed OTC labeling, DFL and CIL are provided in Appendix 1 and Appendix 2, respectively. The prescription labeling (USPI) for Nasacort AQ is provided in Appendix 3.

1.1 ALLERGIC RHINITIS AND UNMET MEDICAL NEED

Allergic rhinitis is an immunoglobulin E (IgE) mediated inflammatory response to airborne allergens which is marked by a symptom complex of nasal congestion (stuffiness), rhinorrhea/discharge (runny nose), sneezing, nasal pruritus (itchiness), and eye symptoms. Less commonly associated symptoms include headache, cough and itchy throat. AR can present itself as seasonal AR (SAR) due to sensitivity to seasonal outdoor allergens such as tree pollen or perennial AR (PAR) which reflects sensitivity to a more constant exposure to indoor allergens such as animal dander. SAR or PAR is often referred to as hay fever or upper respiratory allergies in the approved labeling for OTC AR medications.

The clinical symptoms of nasal congestion, runny nose, sneezing and itchy nose in the setting of allergen exposure is often sufficient to identify AR. With the exception of allergists, few health care professionals routinely use skin or blood tests to confirm a diagnosis of AR (1). AR is a well established OTC indication and consumers can also self-recognize nasal allergies from these clinical symptoms. A number of OTC products, both oral dosage forms (e.g., tablet) and nasal sprays, are already approved for consumer self-treatment of AR.

Inadequate treatment of AR across all age groups, is associated with fatigue, sleep disturbance, substantial negative impacts on quality of life, psychological well-being and the ability to learn and process cognitive input. Approximately one third of patients with AR report that AR symptoms have caused them to miss work and half reported that AR affects their daily lives to some or to a moderate extent (2). In children, AR interferes with their quality of sleep, their outdoor activities, and even their performance at school (1).

Approved OTC products indicated for treatment of AR include oral antihistamines, oral/intranasal decongestants and nasal chromones. Nasal chromones, need to be used multiple times a day. The most commonly used OTC medication class is oral antihistamines. However, oral antihistamines are not indicated for the treatment of nasal congestion which is the most bothersome AR symptom. Many oral antihistamines also cause sedation which can interfere with driving or work activities. When using oral antihistamines some children experience excitability.

Decongestants can reduce nasal congestion. Pseudoephedrine, one of the most effective decongestants, has restricted availability because of its potential for diversion as it can be converted to methamphetamine. In some states pseudoephedrine containing products require a

prescription. Nasal spray decongestants, such as oxymetazoline, can be effective in reducing nasal congestion but should not be used for more than 3 days as they may cause a rebound effect called rhinitis medicamentosa. Products containing decongestants may not be appropriate for all consumers. Many require consultation with a physician before use if the consumer has common medical conditions including high blood pressure, heart disease and diabetes. For children, there are age restrictions for many decongestant products when used as a single agent and in combination with antihistamines.

Thus, there is a need for consumer OTC products for adults and children that can reduce AR symptoms including nasal congestion. In randomized placebo-controlled studies, INS, including Nasacort AQ, have been shown to be highly effective in treating AR and reducing nasal congestion, which is regarded as the most bothersome AR symptom (3). Nasacort AQ has demonstrated greater improvements in nasal AR symptoms and greater improvements in quality of life compared to loratadine (Claritin®), a second generation oral antihistamine (4).

The most recent treatment guideline for the treatment of AR (5) by the Joint Task Force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology states that INS are the most effective treatment class of medication for AR. While there are many approved prescription INS products, there are no INS products approved for OTC use in the US. The switch of Nasacort AQ to OTC status would offer a new consumer option for treatment of AR with a highly effective medication, especially for nasal congestion.

1.2 PHARMACOLOGICAL PROFILE OF TRIAMCINOLONE ACETONIDE

TAA is a synthetic fluorinated corticosteroid with moderate potency compared to other intranasal steroids (6). Although the precise anti-allergic mechanism of corticosteroids is unknown, corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

Following recommended daily intranasal administration of 220 mcg to adult or 110 mcg to pediatric AR patients, systemic exposure to TAA is minimal due to limited TAA absorption and rapid and extensive metabolism of TAA. The terminal half-life ($t_{1/2}$) is 3.1 hours and there is no accumulation on repeat dosing of TAA-AQ. Plasma TAA levels are similar for adult AR patients and pediatric AR patients aged 6-12 following administration of 440 mcg (twice the maximum dose). In children aged 2 through 5, the pharmacokinetics of TAA-AQ 110 mcg/day is similar to that in adults dosed at 220 mcg.

Pharmacodynamic effects of TAA-AQ on AR were investigated in a randomized double-blind study of treatment with intranasal TAA-AQ, oral TAA and placebo in subjects with AR. The study demonstrated that the therapeutic efficacy of intranasal TAA-AQ can be attributed to the topical effect of TAA in the nose. The potential effects of TAA-AQ on hypothalamic pituitary adrenal (HPA) axis and pediatric growth have been investigated in randomized placebo-controlled studies and are discussed under safety in Section 4.2.

1.3 SUMMMARY OF NASACORT AQ EFFICACY AND QUALITY OF LIFE ASSESSMENTS

In the NDA and supplemental NDA (sNDA) supporting approval for prescription use in children, adolescent and adults, findings from 13 randomized placebo-controlled trials supported efficacy in reducing nasal symptoms of nasal stuffiness (nasal congestion), nasal discharge (runny nose), sneezing, and nasal itching (itchy nose). Of the 13 studies, 10 enrolled subjects with seasonal AR and 3 enrolled subjects with perennial AR. Across the studies, rhinitis symptoms were rated daily by the subjects during the baseline and double-blind treatment phases.

In the efficacy studies, the primary evaluation period ranged from 2 to 4 weeks. For the treatment of AR in adults and adolescents 12 years of age and older, TAA-AQ 220 mcg was found to significantly improve the nasal index scores and most of its components compared to placebo in all but one study. In the one study that did not achieve a statistical difference between TAA-AQ and placebo, the findings trended in favor of TAA-AQ. Two studies in children 6 through 11 years of age demonstrated statistically significant improvements compared to placebo. In a study of children aged 2 through 5 treated with TAA-AQ 110 mcg, statistically significant improvements of symptoms were observed. Long term efficacy with Nasacort AQ treatment was confirmed by an extended double-blind to a 12-week study in children aged 6 through 11 and by open label extensions to studies in adults/adolescents for one year and in children aged 2 through 5 for 6 months.

The clinical program also included three studies of the effects of TAA-AQ on quality of life (QoL). In two randomized, double-blind, double-dummy, parallel-group studies in adults, subjects in the TAA-AQ groups achieved significant reduction in nasal symptoms and significant improvement in quality of life (per validated instrument Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)), compared to those in loratadine groups during the 4-week treatment period. Another study in adults demonstrated significant improvement in quality of life in subjects treated with TAA-AQ, as evaluated by the validated Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ).

1.4 SUMMARY OF NASACORT AQ SAFETY

The safety profile of Nasacort AQ has been well established in clinical studies and extensive (>16 years) post-marketing experience. In 43 clinical studies, a total of 5558 subjects including 1204 children aged 2 through 11 years treated with Nasacort AQ were evaluated. According to Intercontinental Medical Statistics (IMS) Health data, from April 2000 through March 2012, more than 122 million TAA-AQ bottles were distributed globally with more than 50 million bottles sold in the US. Overall the most frequently reported AEs were local nasal events (such as epistaxis, nasal discomfort) or AEs associated with the underlying AR condition including headache, nasal congestion.

Adverse events of special interest (AESI) were identified based on both the known effects of corticosteroids and the local nasal administration route of TAA-AQ. These were methodically evaluated for TAA-AQ from the clinical trials, published literature, and post-marketing experience and are summarized below:

- Epistaxis was the most common local adverse event reported. Nasal septum perforation was uncommon.

- Ocular adverse events (glaucoma/increased intraocular pressure (IOP) and cataract) were not common.
- No safety signals were identified with regards to immunosuppression, including opportunistic infections.
- Four specific studies were conducted to evaluate the effect of Nasacort AQ treatment on the HPA axis. At therapeutic doses, Nasacort AQ has a low potential to suppress the HPA axis in adults/adolescents or children aged 2 through 11.
- In a study in prepubescent children, a 0.45 cm reduction in 1 year growth rate in the TAA-AQ treatment group was observed and was statistically significant when compared to placebo. Following TAA-AQ discontinuation after 1 year, growth velocity approximated baseline velocity.
- No signal for bone or glucose metabolism effects was observed.

1.5 OVERVIEW OF OTC DEVELOPMENT PROGRAM

The program for the OTC switch of Nasacort AQ from prescription to OTC status aimed to develop a label that consumers could understand, so that it could guide their appropriate use of the medication without the intervention of a physician. The proposed OTC label for Nasacort AQ was based on the prescription label for Nasacort AQ and the labels for existing OTC products indicated for treatment of AR, and input from the FDA.

The proposed OTC labeling for Nasacort AQ consists of two parts: the Drug Facts Label (DFL) and a Consumer Information Leaflet (CIL). The DFL, which is mandated for all OTC medications, appears on the outer carton and on the immediate container of the product (i.e., the bottle). It communicates the indication, directions for use, and warnings. Its format is highly standardized and regulated (Code of Federal Regulations § 201.66). The CIL contains supplementary information primarily focused on use and maintenance of the spray bottle and is included as an insert in the proposed OTC package.

FDA advised that AR is already an established OTC indication, that consumers already successfully self-treat AR with nasal sprays, and that the proposed OTC label for Nasacort AQ largely consisted of elements already present for marketed OTC products. Accordingly, FDA advised that label comprehension studies should focus on the priming of the Nasacort AQ pump, which was a more unique aspect of consumer directions. FDA also requested a human factors study to assess consumers' performance in these tasks. Self-selection and actual consumer use studies were not deemed necessary given the experience with other OTC products and labels, including those for OTC AR products.

Label Comprehension Studies

Multiple label comprehension studies were conducted to assess consumer understanding of the proposed labeling for Nasacort AQ. The Drug Facts Label (DFL) and the Consumer Information Leaflet (CIL) were tested in separate, parallel studies, in order to avoid testing fatigue among participants. Statements communicating potential effects on children's growth velocity, which were developed later than the main DFL, were tested in separate studies, but in the context of the full DFL. Each of these parts of labeling (DFL, CIL, and Growth statements in DFL) were tested

in two phases, to allow for iterative improvement and re-testing of the label content based on initial results and consumer feedback. In all, over 2,000 consumers participated in the label comprehension testing program.

Label comprehension studies of the DFL and CIL were conducted in a general population sample recruited from multiple retail centers across the US. The studies used an iterative process whereby initial testing in Phase 1 led to modifications in the DFL and CIL that were then retested in Phase 2. The testing covered label statements including Uses, Warnings, and Directions. Per FDA recommendations, the primary objectives focused on comprehension of DFL and CIL statements indicating that the Nasacort AQ bottle needed to be primed before first use, as this instruction was regarded as most unique to OTC labeling. Per FDA Guidance for Industry (7) entitled "Label Comprehension Studies for Nonprescription Drug Products," target performance levels were set for comprehension of the primary end-points. The target level was set to 80%, reflecting the low risk associated with failing to prime the pump. The Guidance requires that the lower bound of the 2-sided 95% confidence interval must equal or exceed the target 80%.

In Phase 2, consumer comprehension met the pre-specified success criteria for the primary end-point (priming the pump for first use) each for the DFL (86.8%; 95% CI: 82.6%-90.3%) and for the CIL (88.6%; 95% CI: 85.1%-91.5%). Although not required, it was considered desirable that the secondary and other communication end-points also meet the same success criteria. All secondary endpoints met this statistical criterion of performance (lower bound of the 95% CI at least 80%). In total, 27 of the 28 DFL and CIL label statements (primary, secondary and other communication endpoints) tested met this criterion, with a lower bound of the 95% CI at least 80%. The one exception was a statement saying that it may take a week to achieve around-the-clock relief, which was understood by 83% of respondents. Across all 28 label statements, the average comprehension level for the whole sample was 92%. Among the subset of respondents with low health literacy (as determined by the rapid estimate of adult literacy in medicine (REALM) test), the average comprehension level was 87%. These studies demonstrated that the proposed Nasacort AQ label is well understood.

Two statements regarding growth in children were subsequently added to the DFL. The statements are intended to inform parents of potential growth effects, and to recommend that they inform the child's doctor to facilitate a discussion of growth effects. The statements were also tested, revised and retested in an iterative process. The instruction to tell the child's doctor when the child starts using Nasacort AQ was understood by 96.6% of participants (95% CI: 93.9%, 98.3%). The informational statement that this medication may temporarily slow the rate of growth in some children was understood by 78.7% (95% CI: 73.7%, 83.1%) of the participants. Of these two communication messages, the more important message is to tell the child's doctor at the start of using the medication, and that message was understood by nearly all participants.

Human Factors Study

At FDA's request, an observational human factors study of consumers' ability to prepare, maintain (reprime) and clean the Nasacort AQ pump was conducted. A total of 16-20 subjects from each of the following groups were enrolled: caregivers, (who would be administering the medication to a young child), youth users (who might be administering the medication to

themselves, but possibly with adult supervision), and adult users (who would be administering medication to themselves). Participants reviewed the CIL and then were observed performing priming and cleaning of the nozzle, with their performance scored by observers. The protocol tested three tasks: Initially priming the pump, repriming the pump after a period of non-use, and cleaning the nozzle if it became clogged. Each task was composed of 4 to 6 discrete steps that were evaluated, with a focus on what were considered critical steps. A total of 82% (42/51) demonstrated the ability to activate the spray nozzle until a fine mist was produced during initial priming; 85% (44/52) did so in re-priming. Overall, 76% (37/49) demonstrated cleaning the nozzle by rinsing the spray nozzle under warm water followed by re-priming of the pump. Importantly, none of the missed steps in performance was considered to expose users to any risk. The study demonstrated that consumers using the CIL could adequately prepare and maintain the spray nozzle.

1.6 BENEFIT RISK DISCUSSION

Allergic rhinitis is an IgE mediated inflammatory response to aeroallergens (e.g., pollen, animal dander) that is a highly prevalent condition, affecting up to 60 million Americans (8) (9). This inflammatory condition is characterized by nasal and ocular symptoms which are associated with sleep disturbance, impaired performance and productivity, and a substantially negative impact on quality of life, affecting emotional well-being and social behavior (10) (1).

Medical Need for OTC Availability of Nasacort AQ

AR (i.e., 'hay fever and other upper respiratory allergies') is considered by the FDA as a condition that is self-recognizable and self-treatable. Consumers can easily self-recognize nasal allergies from the clinical symptoms of nasal congestion, runny nose, sneezing and itchy nose. A number of OTC products, both oral dosage forms (e.g. tablet) and nasal sprays, are already approved by the FDA for consumers to self-treat their AR symptoms but these products have limitations.

- Oral antihistamines (OAH) are the most common OTC medication class used by consumers, but they are not indicated for the treatment of nasal congestion. Many OAH cause sedation, which can interfere with driving or work or can cause excitability, especially in children.
- OTC oral decongestants, such as pseudoephedrine, can reduce nasal congestion. But pseudoephedrine, which data suggests is more effective than phenylephrine (11), has restricted consumer availability because of its potential for diversion to the manufacture of methamphetamine. In some states pseudoephedrine is only available by prescription. Additionally, pseudoephedrine products include warnings to ask a doctor before use if a consumer has any of the following conditions: heart disease, thyroid disease, glaucoma, high blood pressure, diabetes or trouble urinating due to an enlarged prostate.
- Intranasal decongestants, such as oxymetazoline, are effective, but should not be used beyond 3 days because of the potential for rebound symptoms, 'rhinitis medicamentosa.' The phenylephrine nasal drops for children need to be used multiple times a day.
- Oral antihistamines are also available OTC combined with oral decongestants. But, as noted for single agent oral decongestants, all such products face increasing restrictions to

access and include age restrictions for children and warnings for consumers with certain health conditions.

- A chromone nasal spray is available for use down to age 2 but needs to be taken 3-4 times per day.

A majority of consumers who have received a diagnosis of AR from a HCP actually use an OTC medication for treatment of their AR symptoms. However, while consumers report that effectiveness is the most important feature of nasal allergy treatments (12), many are not very satisfied with current OTC products. Among AR patients who had used an OTC product for nasal allergy symptoms in the past four weeks, less than half (41%) said they were very satisfied with the medicine they used (13).

Among prescription and OTC pharmacotherapies, intranasal corticosteroids are considered the most effective medication class for treatment of AR by the allergy professional societies (5). Corticosteroids are distinct from antihistamines. They have actions on many inflammatory cells and mediators and inflammation is an important etiology of allergic rhinitis. INS products such as Nasacort AQ effectively treat all 4 nasal allergy symptoms, including nasal congestion.

Nasacort AQ Nasal Spray: Overview, Efficacy and Safety

Triamcinolone acetonide (TAA), the active ingredient in Nasacort AQ, is a well characterized corticosteroid that has been included in numerous prescription products. As an intranasal product, TAA is targeted to the nasal mucosa, where nasal allergies start. Targeting therapy to the nasal mucosa reduces systemic TAA exposure and with it, the potential for systemic side effects. After intranasal administration, TAA is detectable in the plasma, however, with its short terminal half-life of ~3 hours it becomes undetectable within the 24 hours dosing interval. Further, there is no accumulation with repeat daily dosing. Nasacort AQ is not an anabolic steroid. It has no muscle building properties, no immediate psychoactive effects, is not habit forming, and results in no rebound effects or sedation. In the event that the entire contents of the bottle (~9 mg of TAA) were administered all at once, via either oral or nasal application, clinically significant systemic adverse events would most likely not result.

The efficacy of Nasacort AQ, administered once daily for the treatment of AR, is confirmed by 13 studies in adults, adolescents and children to the age of 2 that supported the prescription approvals in those populations. Studies demonstrated that nasal symptoms improved within the first day of use but that one week of daily use may be needed to obtain maximum benefit. Improvements in quality of life with Nasacort AQ have been demonstrated in studies of adults with seasonal AR. In two double-blind, double-dummy studies Nasacort AQ provided significantly greater relief of nasal AR symptoms and greater improvements in quality of life by a validated scale compared to an oral antihistamine. In an open-label study, Nasacort AQ improved nocturnal quality of life and sleep, as assessed by validated scales.

As a targeted therapy to the nasal mucosa, the most common adverse effects of Nasacort AQ are local, particularly in the nose and throat, including epistaxis and nasal discomfort. Nosebleeds (epistaxis) are a very common event in the general population, even without AR. Epistaxis is obvious to the individual, ranging from a few flecks of blood to a frank nosebleed. Nasal septum perforations are uncommon with Nasacort AQ.

Immunosuppression, opportunistic infections, or worsening of infections such as measles, tuberculosis, and chickenpox have not been reported with Nasacort AQ. Specific studies have demonstrated that Nasacort AQ has a low potential to suppress the HPA axis in all age groups.

In a study to evaluate the effects of Nasacort AQ on pediatric growth rate, an effect on growth velocity (less than ¼ inch) was detected in pre-pubertal children with perennial AR who were treated with Nasacort AQ 110 mcg daily for one year. Effects on growth velocity have been observed with other INS. The study did not follow children to attainment of adult height, therefore, the potential effect on final adult height is not known. The effect detected in the study by comparison of two groups (Nasacort AQ and placebo) may not be discernible in an individual child in the clinical practice setting. Nevertheless, a direction has been included in the proposed DFL for the parent to inform the child's doctor about use of Nasacort AQ. It is anticipated that regular well-child visits will continue when Nasacort AQ is used in the OTC environment.

Hypersensitivity reactions have been reported with use of the product and those with a history of allergic reactions to triamcinolone acetonide or any of the nasal spray ingredients should not use Nasacort AQ. No signal for bone or glucose metabolism effects was observed. Some cases of increased intraocular pressure/glaucoma and cataracts have been reported over the 16 years of market use. Hence, the proposed OTC labeling informs consumers who have or had glaucoma or cataracts to ask a doctor before use of Nasacort AQ.

Nasacort AQ in the OTC Environment

An OTC label has been developed to restate information from the USPI in language that is well understood by the consumer. Label comprehension studies support that consumers, even those with low health literacy, can understand the instructions in the proposed consumer label. The DFL includes specific sections for Purpose, Uses, Warnings and Directions and the Consumer Information Leaflet provides directions and illustrations for use and maintenance of the nasal spray. These label directions will help mitigate potential risks with use of Nasacort AQ in the consumer environment.

The directions for dosing of OTC Nasacort AQ, as for the prescription product, are simple, one or two sprays per nostril once daily, and were well understood by consumers. In the prescription environment, there were few reports of abuse, or of taking excessive amounts.

Nasacort AQ Nasal Spray is a monotherapy which effectively treats all four nasal symptoms of allergic rhinitis, including nasal congestion, the symptom that sufferers find most bothersome. The efficacy and safety of the product has been characterized in multiple clinical studies in adults and children as well as with market experience for over 16 years. The proposed OTC labeling has been developed to ensure consumer understanding of the proper use of the product and to help mitigate potential safety risks. Studies have confirmed consumer understanding of the proposed label.

Overall, the OTC availability of Nasacort AQ will improve access to the most effective class of nasal allergy medications, without the requirement for a prescription or physician visit, giving consumers an additional OTC choice for treatment of nasal allergy symptoms. This expanded access for both adults and children has the potential to improve health outcomes in these consumers and may have secondary beneficial impacts on the quality of life of these nasal allergy sufferers.

Sanofi acknowledges that there are different considerations when evaluating the benefits and risks for adults versus the pediatric populations. For adults, the post-marketing safety data for Nasacort AQ is favorable. In the OTC environment, there is a clear need for a more effective AR remedy that treats all four nasal symptoms and Nasacort AQ would address this need. The OTC availability would introduce few risks and these would be mitigated by the OTC labeling. Therefore, the benefits far outweigh the risks for adults.

For children, there is also a clear need for a more effective AR remedy and Nasacort AQ would address this need. The post-marketing safety data for Nasacort AQ is favorable. Although the potential effect on growth requires additional consideration, it does not appear that it is an issue that the OTC availability will impact in an unfavorable way. This is because, despite the fact that the growth study demonstrated an effect in the Nasacort AQ treatment group, this effect is quite small and unlikely to be detectable in an individual child. Therefore, it would almost never be the reason for a change in the treatment management by a child's physician, even in a prescription setting.

In summary, the potential safety risks of Nasacort AQ without physician oversight would not be different or greater than those that currently exist with Nasacort AQ as a prescription product, where Nasacort AQ has demonstrated a favorable benefit-risk profile. These risks are manageable through the OTC labeling. Therefore, the benefits of OTC access to a more effective treatment for AR outweighs the risks in both adults and children.

2 BACKGROUND INFORMATION

Nasacort® AQ Nasal Spray is an aqueous suspension of triamcinolone acetonide (TAA) [Nasacort AQ or TAA-AQ will be used interchangeably in this briefing document]. Sanofi-aventis U.S. LLC and Chattem Inc., each A SANOFI COMPANY hereby referred to as Sanofi, submitted an application to the FDA with data supporting a switch of Nasacort AQ from prescription (Rx) to OTC status.

2.1 REGULATORY HISTORY

In the US, TAA is approved for oral treatment (i.e., tablet, syrup), by injection (i.e., intra-articular, intramuscular, intravitreal), by oral or nasal inhalation (i.e., aerosol, aqueous nasal spray), and as a topical cream or ointment. TAA formulations (tablets, creams, ointment, injectable,) are also approved worldwide. Triamcinolone acetonide has a long history of use in asthma and AR indications in the US. Sanofi has registered multiple inhaled and intranasal formulations of TAA. For AR, TAA was first approved as a nasal aerosol formulation containing chlorofluorocarbon (CFC) on 11 July 1991 (Nasacort Nasal Inhaler). Subsequently, an aqueous formulation of TAA, Nasacort AQ, was approved on 20 May 1996 for the same indication. There is extensive post-marketing experience with TAA.

2.1.1 Nasacort AQ (US)

Nasacort AQ which is the product under discussion for Rx-to-OTC switch is currently approved as a prescription product in the US for intranasal administration to treat nasal symptoms of seasonal and perennial allergic rhinitis (AR). Nasacort AQ was approved in the US in 1996 for use in adults and adolescents 12 years of age and older. In 1997, the indication was extended to children 6 through 11 years of age and in 2008 the indication was extended to children 2 through 5 years of age, based on submission of new data on children in those age ranges.

Each actuation of the metered dose pump delivers 55 mcg of TAA per spray. The recommended dosing by age is as follows:

- In adults and adolescents (≥ 12 years), the starting and maximum dose is two sprays in each nostril once daily (220 mcg/day). When symptoms are controlled, the dose may be reduced to one spray in each nostril once daily (110 mcg/day).

- For children 6 through 11 years of age, the starting dose is one spray in each nostril once daily (110 mcg/day) with a maximum dose of two sprays in each nostril once daily (220 mcg/day).

- For children 2 through 5 years of age, the starting and maximum dose is one spray in each nostril once daily (110 mcg/day).

The proposed OTC indication is for temporary relief of hay fever or other upper respiratory allergies (nasal congestion, runny nose, sneezing, and itchy nose) in children 2 years of age and older, adolescents and adults. The proposed OTC product is the same formulation and spray

pump with the same dosing instructions as the currently approved Nasacort AQ. The text of the dosing instructions has been simplified for the OTC label. The Nasacort AQ product is shown in Figure 1.

Figure 1 - Nasacort AQ Product

2.1.2 Nasacort AQ (Outside the US)

Nasacort AQ is currently approved as a prescription drug to treat nasal symptoms of AR in more than 60 countries and for nonprescription use in 11 countries (Table 1).

Table 1 - Countries where TAA-AQ is approved for nonprescription use

Country	Available without Prescription	Approval Year for Nonprescription use	Indication
Australia	**Pharmacy Medicine – Sold without supervision of pharmacist**	2004	SAR* and PAR** in adults and children 12 years and older
Denmark	Pharmacy Medicine – Sold with supervision of pharmacist	2013	SAR in adults 18 years of age and older
Finland	**Pharmacy Medicine – Sold without supervision of pharmacist**	2009	SAR in adults 18 years of age and older
Malaysia	Pharmacy Medicine – Sold with supervision of pharmacist	1998***	SAR and PAR in adults and children 2 years of age and older
Malta	Pharmacy Medicine – Sold with supervision of pharmacist	2009	SAR in adults 18 years of age and older
New Zealand	**Pharmacy Medicine – Sold without supervision of pharmacist**	2004	SAR and PAR in adults and children 6 years of age and older
Norway	**Pharmacy Medicine – Sold without supervision of pharmacist**	2010	SAR in adults 18 years of age and older
Sweden	**Pharmacy Medicine – Sold without supervision of pharmacist**	2010	SAR in adults 18 years of age and older
Switzerland	Pharmacy Medicine – Sold with supervision of pharmacist	2010	SAR in adults 18 years of age and older
UK	Pharmacy Medicine –Sold with supervision of pharmacist	2001	SAR in adults 18 years of age and older
Uruguay	Pharmacy Medicine –Sold with supervision of pharmacist	1995***	SAR and PAR in adults and children 2 years of age and older

* SAR – Seasonal Allergic Rhinitis
** PAR – Perennial Allergic Rhinitis
*** First approval date for adult and adolescent indication. Following the first approval, the pediatric indication was approved as data became available in this population similar to US.
Bold represents countries where the product is sold without the supervision of a pharmacist.

In 5 of the 11 countries (Table 1), a pharmacist is not required to obtain Nasacort AQ. In the remaining countries, a pharmacist is required for the consumer to obtain the product. As a nonprescription product, Nasacort AQ was approved for various ages depending on regional Health Authority requirements and the labeling of other already approved INS nonprescription products in those countries.

2.2 INTERACTIONS WITH THE AGENCY FOR RX-TO-OTC SWITCH

In support of the Rx-to-OTC switch, Sanofi had several interactions with the FDA to discuss the overall switch strategy, content of the submission and the consumer studies that would be required. No new clinical studies were required by the FDA to support the switch. A complete

review of the safety and efficacy of Nasacort AQ from clinical studies and post-marketing surveillance was provided in the switch application. The FDA advice and interactions pertaining to consumer studies are discussed in Section 5.1.

A key consideration in the switch approval of Nasacort AQ is the age recommendation for OTC use. Sanofi initially proposed to the FDA that the OTC indication be restricted to 18 years of age and older. FDA did not agree, indicating that they were unaware of any data that would preclude OTC approval for the full age range of 2 years and older, and requested a justification for an age restriction. Sanofi conducted a comprehensive review of Nasacort AQ safety information including for the pediatric population. The findings from this review are provided in Section 4 of the briefing book. In light of the benefits of OTC access, the safety evaluation and consistent with the FDA's recommendation, Sanofi filed for a full switch (2 years of age and older) where the indication, population and duration of use reflect the current approved prescription labeling.

2.3 MEDICAL NEED FOR OTC NASACORT AQ IN ALLERGIC RHINITIS

Allergic rhinitis is an immunoglobulin E (IgE) mediated inflammatory response to airborne allergens which is marked by a symptom complex of nasal congestion (stuffiness), rhinorrhea/discharge (runny nose), sneezing, nasal pruritus (itchiness) and watery itchy eyes. Other symptoms may include headache, cough, and itchy throat. AR is a highly prevalent condition in adults and children, and it is estimated that nearly 60 million people in United States suffer from AR each year (8) (9).

AR is often described within the US medical community as seasonal AR (SAR) or perennial AR (PAR). SAR is due to sensitivity to seasonal outdoor allergens such as tree pollen. PAR reflects sensitivity to more constant exposure to indoor allergens, such as animal dander. Individuals may have SAR, PAR or a mix of the two. In a survey of adults that had nasal allergy symptoms in the past year or were taking allergy medication, 56% reported year round allergy symptoms. In the parallel survey, HCPs indicated that more than 60% patients have severe or moderate symptoms (2). SAR or PAR is often referred to as hay fever or upper respiratory allergies in the approved labeling for OTC AR medications.

The clinical symptoms of nasal congestion, runny nose, sneezing and itchy nose in the setting of allergen exposure is often sufficient to identify AR. With the exception of allergists, few health care professionals routinely use skin or blood tests to confirm a diagnosis of AR (1). AR is a well established OTC indication and in turn, consumers are able to self-recognize nasal allergies from these clinical symptoms. A number of OTC products, both oral dosage forms (e.g. tablet) and nasal sprays, are already approved for consumer's self-treatment of AR.

AR is one of the most common chronic conditions in the United States (14). It disrupts life and causes significant discomfort to those with the condition. Inadequate treatment of AR across all age groups is associated with fatigue, sleep disturbance, substantial negative impacts on quality of life, psychological well-being and the ability to learn and process cognitive input. Approximately one third (~30%) of patients with AR report that AR symptoms have caused them to miss work and half (~51%) reported that AR affects their daily lives to some or to a moderate extent (2). In children, AR interferes with quality of sleep, outdoor activities, and even performance at school (1). In a survey of parents of children with and without allergic rhinitis, parents of children with allergies were more than twice as likely to report sleep problems (e.g.,

difficulty falling asleep, waking during the night, and lack of a good night's sleep) in their children than parents of allergy-free children. In addition, a large percentage (40%) of parents reported their child's AR interfered with their school performance and general outdoor activities were limited 3 to 4 times more frequently in children with nasal allergies than in allergy-free children (1).

Approved OTC products for AR include oral antihistamines, oral/intranasal decongestants and nasal chromones. The most commonly used OTC medication class is oral antihistamines. However, oral antihistamines are not indicated for the treatment of nasal congestion which is the most bothersome AR symptom. Some antihistamine products may cause drowsiness which can impair ability to drive and work and may cause excitability, especially in children.

Decongestants can reduce nasal congestion. However, pseudoephedrine, one of the most effective decongestants (11) has restricted availability because of its potential for diversion to the manufacture of methamphetamine. In some states, pseudoephedrine is only available by prescription. Pseudoephedrine may cause nervousness and insomnia. Phenylephrine is another OTC oral decongestant with minimal clinical efficacy (11). Local nasal spray decongestants, such as oxymetazoline, can be effective in reducing nasal congestion but should not be used for more than 3 days as they may cause a rebound effect called rhinitis medicamentosa. Products containing decongestants may not be appropriate for all consumers. Many are restricted by age and require consultation with a physician before use if the consumer has common medical conditions including high blood pressure, heart disease, diabetes, thyroid disease and difficulty urinating.

For the pediatric population, OTC products are available but have certain limitations. Intranasal cromolyn is available OTC but needs to be taken every 4 – 6 hours a day. There are OTC once-a-day antihistamines available for children down to age 2, but they are not indicated for congestion, requiring another medication for full nasal allergy symptom relief. Some OTC decongestants including, pediatric phenylephrine nose drops, can be used down to age 2, but must be applied several times a day. Oral OTC products that combine antihistamines and decongestants have age restrictions. Combination products containing first generation antihistamines are indicated down to age 6, without consulting a doctor. Combination products containing second generation antihistamines are either not to be used by children under age 12 or first require consultation with a doctor.

Among AR patients, who had used an OTC for nasal allergy symptoms in the past four weeks, less than half (41%) said they were very satisfied with the medicine they used (13). Thus, there is a need for consumer OTC products that can reduce AR symptoms including nasal congestion providing consumers with additional options for treatment.

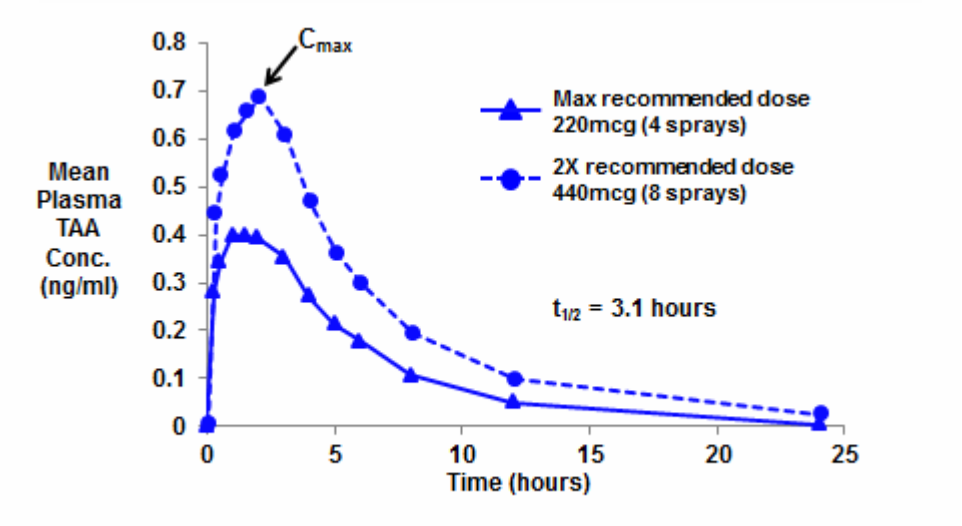
Intranasal steroids (INS) are considered by the allergy professional societies as the most efficacious class of medicines for controlling AR symptoms in both adults and children (5). INS reduces all nasal symptoms of AR, including nasal congestion. While there are many approved prescription INS products, there are no INS products approved for OTC use in the US. The switch of Nasacort AQ to OTC status will offer a new consumer option for the treatment of AR with a highly effective medication, especially for nasal congestion.

2.4 PHARMACOLOGICAL PROFILE OF TRIAMCINOLONE ACETONIDE

TAA is a synthetic fluorinated corticosteroid with approximately 8 times the potency of prednisone in animal models of inflammation. Although the precise mechanism of corticosteroid antiallergic action is unknown, corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

Pharmacokinetic and pharmacodynamic studies of TAA-AQ were conducted in healthy subjects and patients with AR. At the maximum recommended therapeutic dose of 220 mcg, C_{max} occurs at about 1.5 hours with a terminal $t_{1/2}$ of 3.1 hours (Figure 2).

Figure 2 - Plasma Triamcinolone Acetonide Concentration by Time



In repeat dosing studies, no accumulation was observed. Pharmacokinetics (PK) of TAA-AQ in pediatric AR patients 6 through 11 years of age is similar to that of adult AR patients, even when both are administered twice the maximum dose (440 mcg). In children 2 through 5 years old, systemic exposure following TAA-AQ 110 mcg/day is similar to that of a dose of 220 mcg in adults.

Formal drug-drug interactions studies have not been conducted. No drug-drug interactions have been identified with TAA-AQ from clinical trials and no signals for drug-drug interactions have been identified from post-marketing safety data.

In order to determine if systemic absorption plays a role in the effect of TAA-AQ on AR symptoms, a 2-week double-blind, placebo-controlled Study 308 was conducted comparing TAA-AQ intra-nasally administered, orally ingested, and placebo in 297 adult patients with SAR. Nasal symptoms improved with intranasal administration of TAA-AQ. An orally administered dose of TAA-AQ, previously identified to yield a similar PK profile to the intranasal dose, was not effective in relieving nasal symptoms. The study demonstrated that the therapeutic efficacy of intranasal TAA-AQ can be attributed to the topical effect of TAA in the nose.

Four specific pharmacodynamic studies, one in adults and three in children were conducted and confirmed that intranasal TAA-AQ has a low potential for HPA axis suppression. Two specific pharmacodynamic studies in children addressed the potential effects of TAA-AQ on growth. These studies are discussed in more detail in the safety section of this briefing document.

2.5 PRECLINICAL EVALUATION

In preclinical studies conducted by the Sponsor, TAA was not carcinogenic or mutagenic. TAA was teratogenic in rats, rabbits and monkeys. In rats and rabbits, cleft palate, hydrocephaly, and axial skeletal defects were observed at exposure less than and 2 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis. In monkeys, cranial malformations were observed an exposure approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis. Rodents may be more prone to teratogenic effects of corticosteroids than human. These findings are consistent with those observed with other corticosteroids, and TAA-AQ should be used in pregnancy only if the benefit justifies the risk to the fetus. These results are described in the 'Use in Specific Population' of the Nasacort AQ prescription label (USPI) (Appendix 3). For the proposed Nasacort AQ DFL, pregnant or breast feeding women are directed to ask a health care professional before use. This statement is consistent with standard DFL language.

3 EFFICACY FROM CLINICAL STUDIES AND QUALITY OF LIFE ASSESSMENTS

3.1 OVERVIEW OF STUDY DESIGN SUPPORTING EFFICACY

Table 2 provides a listing of the key characteristics of the 13 randomized placebo-controlled studies (10 adult/adolescent studies and 3 studies in children aged 2-11) that confirmed efficacy of TAA-AQ in AR (Appendix 4 provides a detailed summary of each study).

In adults and adolescents, the pivotal studies were 301, 302 and 304 in SAR and 305 in PAR. In children aged 2 through 11, the pivotal studies were 312 in SAR, and 314 and 3502 in PAR. Studies of SAR utilized a 2-3 week study period. Studies of PAR had primary evaluations at 4 weeks of the double blind study period, although study 314 in children extended the double-blind period to 12 weeks and studies 305 (adults/adolescents) and 3502 (children) had open-label extensions to 12 and 6 months, respectively.

All enrolled subjects had to have an allergic etiology for their rhinitis (primarily by wheal responses to dermal skin tests) and were required prior to randomization to demonstrate a minimum score for nasal allergy symptoms, based on daily diary recordings of symptoms. For adult and pediatric studies in general, slightly more males were enrolled than females, except Study 302 (>90% male). In adult/adolescent studies, non-Caucasian subjects ranged from 2-16% and in pediatric studies from 10-34%.

Table 2 - Listing of the 13 Randomized Placebo-Controlled Double Blind Studies that Evaluated the Efficacy of TAA-AQ in Clinical Program

Study number (full name)	Study Type	Subject age (year)	Treatment dose (mcg)	Treatment duration (week) / Number of subjects treated
Studies in Adults and Adolescents				
201 (RG5029Y-201)	SAR, Dose response	18 - 67	TAA-AQ: 27.5, 55, 110, 220, placebo	2 / 360
301 (RG5029Y-301)	SAR - ragweed	20 - 65	TAA-AQ: 220, placebo	2 / 140
302 (RG5029Y-302)	SAR - ragweed	12 - 17	TAA-AQ: 220, placebo	2 / 136
304 (RG5029Y-304)	SAR - Mountain cedar	19 - 74	TAA-AQ: 55, 220, placebo	2 / 206
305 (RG5029Y-305)	PAR	11 - 59	TAA-AQ: 220, placebo	4 / 178
306 (RG5029Y-306)	SAR with possible dose titration after 2 weeks	18 - 82	TAA-AQ: 220/110, placebo, Budesonide 400	4 / 293
307 (RG5029Y-307)	SAR	16 - 66	TAA-AQ: 220, placebo	3 / 81
308 (RG5029Y-308)	SAR – ragweed, Topical vs systemic	18 - 67	TAA-AQ: 220, 275 oral, placebo	2 / 297
309 (RG5029Y-309)	SAR - ragweed with dose titration after 1 week	18 - 79	TAA-AQ: 220/110, 220/220, placebo	3 / 429
313 (RG5029Y-313)	SAR - mountain cedar	18 - 77	TAA-AQ: 220, placebo	2 / 182
Studies in Children 2 through 11				
312 (RG5029Y-312)	SAR - spring grass	6 - 11	TAA-AQ: 110, 220, placebo	2 / 223
314 (RG5029Y-314)	PAR	4 - 12	TAA-AQ: 110, 220, placebo	12 / 319
3502 (XRG5029C/3502)	PAR	2 - 5	TAA-AQ: 110, placebo	4 / 474

Across all studies, nasal stuffiness, nasal discharge, sneezing and nasal itching were rated daily by subjects during the baseline and double-blind treatment phases. Daily diary cards scored

symptoms over the previous 24 hours (reflective scoring) by severity and impact on daily living and sleep using the following 0-3 scale:

- 0 = Symptom absent
- 1 = Mild symptoms (present, but not annoying to self)
- 2 = Moderate symptoms (present and annoying to self, but does not interfere with sleep or daily living)
- 3 = Severe symptoms (present and interferes with sleep/or unable to carry out activities of daily living)

In Studies 313, 314, and 3502, the daily rhinitis symptoms were also rated based upon symptomatology immediately prior to dosing (instantaneous scoring).

The total symptom score was computed using the nasal index score (NI) or the Total Nasal Symptom Score (TNSS). The NI was defined as the sum of nasal stuffiness, nasal discharge and sneezing symptom scores and had a score range of 0 to 9. The TNSS added the nasal itching score to the other 3 symptoms scores captured by NI giving a score range of 0 to 12. Subjects had to meet minimum threshold requirements for entry using symptoms scores over the last 4 baseline days.

The primary efficacy analysis for 12 of the 13 studies was based on the mean change from baseline in 24-hour reflective NI and its 3 components (i.e. nasal stuffiness, nasal discharge, and sneezing) averaged over the primary treatment period. In study 3502, a pediatric study in children aged 2 through 5, the primary efficacy analysis was based on the mean change from baseline in the instantaneous TNSS, averaged over the primary treatment period.

Secondary analyses were performed for the change in primary endpoint and each symptom component by time period (Days 1 to 4 and Weeks 1 to 4) during the double-blind treatment period. Patient and physician global evaluation of efficacy at the end of the double-blind treatment period were additional secondary efficacy variables.

3.2 EFFICACY RESULTS

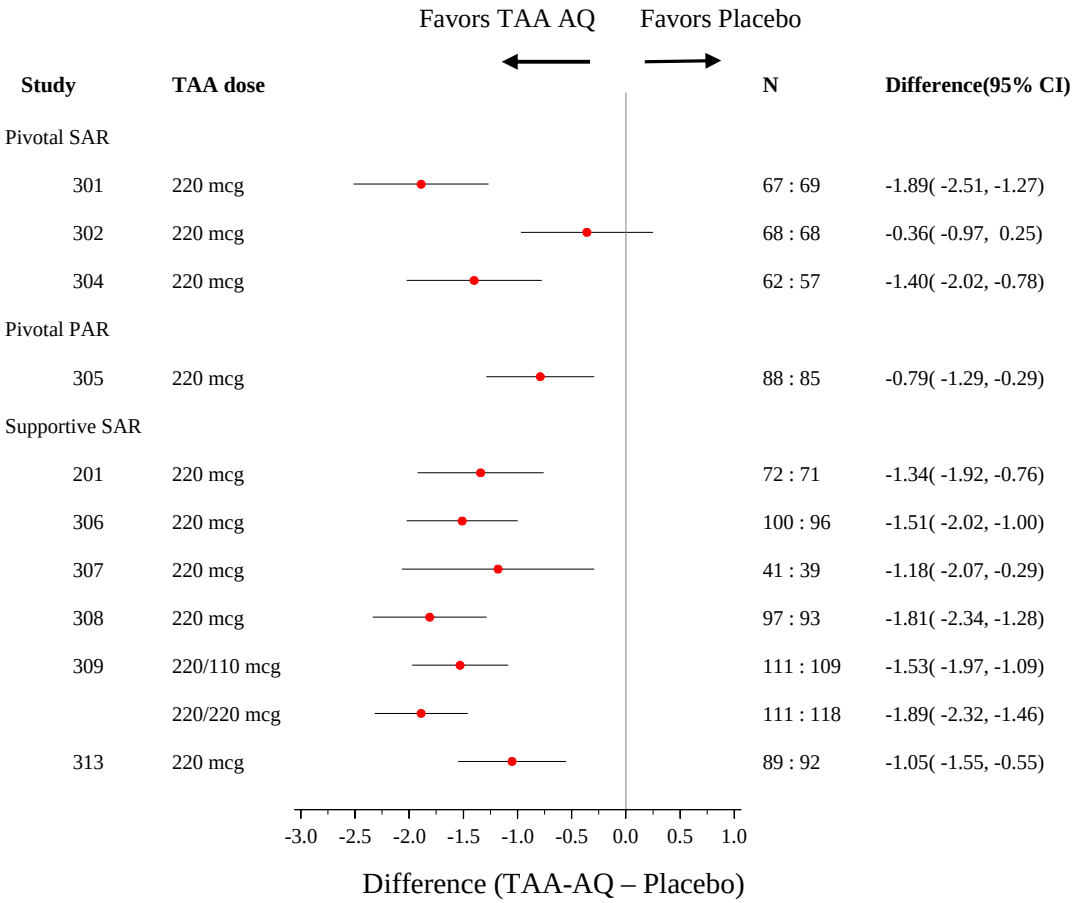
The following figures present the differences between TAA-AQ and placebo across each study for the primary analysis of NI or TNSS based upon reflective scoring, in forest plots. The pediatric age group includes children aged 2 through 11 while adolescents are grouped with adults. Pivotal and supportive studies are grouped based upon type of AR (SAR and PAR) included in each study.

3.2.1 Studies in Adults and Adolescents

In Figure 3, for adults and adolescents, TAA-AQ 220 mcg significantly improved the NI in the pivotal SAR and PAR studies with the exception of Study 302 which demonstrated a non-significant improvement with TAA-AQ. Findings across the supportive SAR studies were consistent with the pivotal findings. Separate analyses of the nasal symptom components in the NI also found significant differences from placebo for most components in each study. In study 309 that examined down titration from 220 to 110 mcg after one week of treatment, TAA-AQ

was also significantly different from placebo. Supporting analyses conducted for separate time periods (Days 1 to 4 or Days 1 to 13, depending upon the study design) and by week (Weeks 1 to 4) also supported the primary findings with efficacy observed within one day. Pooled efficacy analyses supported the primary findings. Additionally, subgroup analyses by age, gender and race supported the primary findings.

Figure 3 - Treatment difference (TAA-Placebo) in change from baseline in 24-hour reflective for nasal index* of adult and adolescent studies



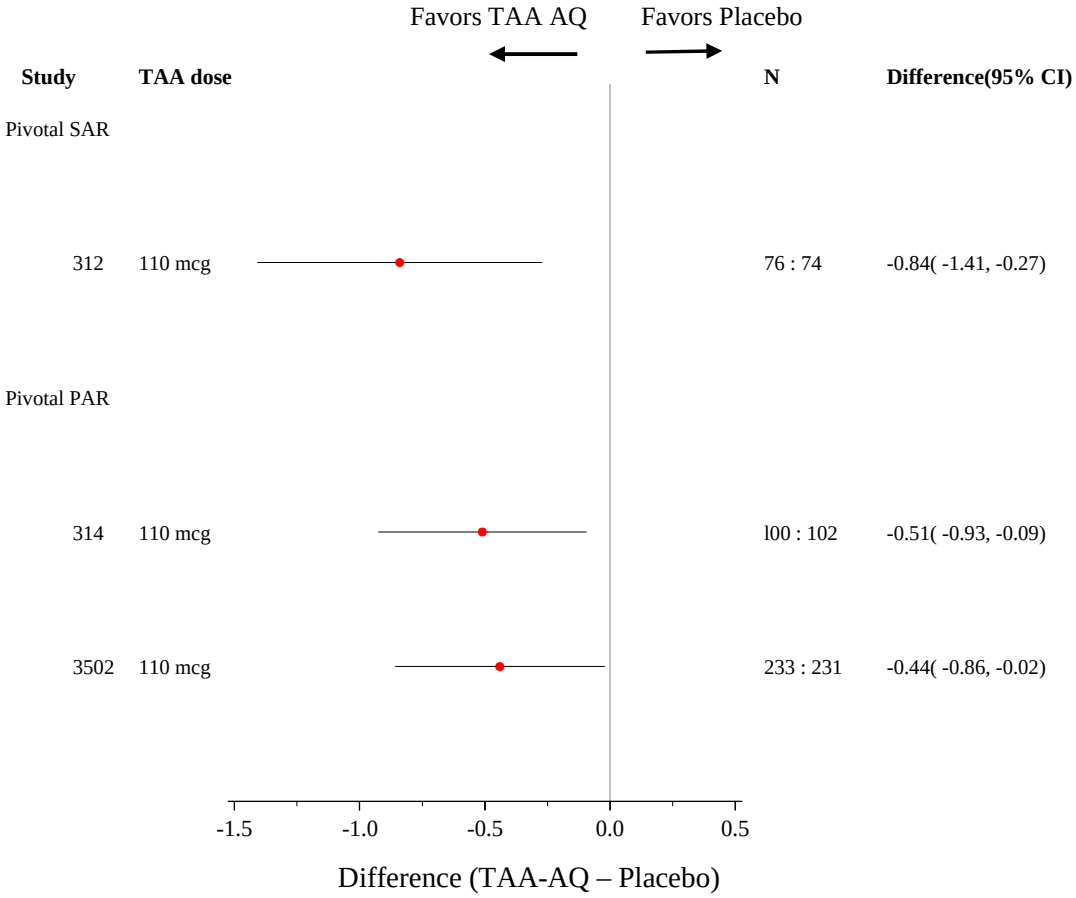
N: Numbers of subjects in placebo vs. TAA-AQ groups.
CI: confidence interval.
*Nasal index is the sum of nasal stuffiness, nasal discharge, and sneezing scores and ranges from 0 to 9.
PGM=DEVOPS/XRG5029/OTCNDA/ISE2012/REPORT/PGM/NASAL_INDEX_forest_adult.sas
OUT=REPORT/OUTPUT/NASAL_INDEX_forest_adult_i.rtf (18JUN2013 - 19:57)

3.2.2 Studies in Children 2 through 11

In Figure 4, for the treatment of SAR and PAR in children aged 6 through 11, TAA-AQ 110 mcg significantly improved the NI score compared to placebo. For the treatment of PAR, with or without symptoms of SAR, in children aged 2 through 5, TAA-AQ 110 mcg significantly improved the TNSS and some of the nasal symptoms, such as sneezing and nasal itching over the 4 week treatment period.

As in adults, separate analyses of symptom components were consistent with the overall analysis. Supporting analyses conducted for separate time periods (Days 1 to 4) and by week (Weeks 1 to 4) also supported the primary findings.

Figure 4 - Treatment difference (TAA-Placebo) in change from baseline in 24-hour reflective for nasal index/TNSS* of studies in children



N: Numbers of subjects in placebo vs. TAA-AQ groups.
CI: confidence interval.
*Nasal index for studies 312, 314; TNSS for study 3502. Nasal index is the sum of nasal stuffiness, nasal discharge, and sneezing scores and ranges from 0 to 9; TNSS is the sum of nasal stuffiness, nasal discharge, sneezing, and nasal itching scores and ranges from 0 to 12.
PGM=DEVOPS/XRG5029/OTCNDA/ISE2012/REPORT/PGM/NASAL_INDEX_forest_ped.sas
OUT=REPORT/OUTPUT/NASAL_INDEX_forest_ped_i.rtf (18JUN2013 - 20:03)

In global evaluation of efficacy by subjects and investigators, both adult and pediatric subjects assigned to TAA-AQ reported significantly more improvement than placebo. Other secondary endpoints also supported the overall effectiveness of TAA-AQ in treating AR. Subgroup analyses of the primary endpoint were consistent with the overall findings.

3.3 OTHER EFFICACY AND QUALITY OF LIFE BENEFITS

Three studies formally examined the effect of treatment with TAA-AQ on quality of life. The first two studies examined the effects of TAA-AQ versus an oral antihistamine, loratadine (Claritin®) on efficacy and quality of life in adults with SAR. The third study evaluated the effect of TAA-AQ on nocturnal quality of life and sleep.

Two studies (4) (15) were randomized, double-blind, double-dummy, parallel group studies in adults comparing the efficacy and quality of life of TAA-AQ 220 mcg to loratadine 10 mg daily for 4 weeks. Allergy symptoms (nasal stuffiness, nasal discharge, nasal itching, sneezing and ocular symptoms) were evaluated in the 0-3 scale, and total nasal symptom score (TNSS) was the sum of the 4 nasal symptoms. In addition, quality of life was evaluated by the validated Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) which included domains for: sleep, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms, activities and emotions.

TAA-AQ, in both studies demonstrated superior improvements compared to loratadine in the TNSS, as well as its individual nasal symptom components. TAA-AQ and loratadine treatment improved ocular symptoms to a similar degree. The mean changes from baseline of TNSS are summarized in Table 3.

Table 3 - Mean change from baseline of TNSS

	TAA-AQ 220 mcg		Loratadine		
	N	Mean change from baseline	N	Mean change from baseline	P-value
Study 601	174	-4.4	174	-3.6	<0.01
Study 602	188	-4.83	189	-3.48	<0.001

In both studies, subjects treated with TAA-AQ reported significantly greater improvements than those treated with loratadine on overall RQLQ score. Additionally, for 3 individual domains, activity, nasal symptoms, and practical problems, TAA-AQ treatment resulted in significantly greater improvement than the active comparator.

The third study was an open-label study (16) examining the effects of TAA-AQ treatment on nocturnal symptoms and sleep in adult AR patients. Six hundred fifty-one patients were treated with TAA-AQ for 3 weeks and were evaluated by the validated scales: Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ) and the Pittsburgh Sleep Quality Index (PSQI). The NRQLQ comprises of 4 domains: problems with sleep, symptoms during sleep, symptoms on waking in the morning, and practical problems (during waking hours). The PSQI is an instrument designed to measure sleep disturbance over the previous month. This instrument consists of 19 items over 7 domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction.

Subjects demonstrated significant improvements in the NRQLQ and all its domains (all $p<0.001$) which correlated with improvements in the PSQI ($p<0.001$). Overall NRQLQ and PSQI scores were improved from baseline by 52% and 29%, respectively.

4 SAFETY

The safety profile of TAA-AQ was evaluated in 43 clinical studies and over 16 years of post-marketing experience including extensive literature screening. The safety section contains a review of the general safety profile including adverse events and serious adverse events (AEs and SAEs) and adverse events of special interest (AESI). In addition the FDA adverse event reporting system (AERS) and World Health Organization (WHO) VigiBase Pharmacovigilance Databases were reviewed for signal detection purposes.

4.1 GENERAL SAFETY FROM CLINICAL STUDIES AND POST-MARKETING EXPERIENCE

4.1.1 Clinical Studies

4.1.1.1 Extent of Exposure

Safety was evaluated in 8925 subjects with 5558 subjects treated with TAA-AQ including 1204 children aged 2 through 11. Of the 43 studies, 16 were randomized placebo-controlled with an integrated clinical database, in which 2 were extended to a long term open-label period of 6-12 months. One randomized placebo-controlled study in children aged 3 through 9 was conducted over a 12 month double-blind treatment period.

4.1.1.2 Adverse Events

Adults and Adolescents

In the randomized placebo-controlled studies in adults and adolescents, AEs as in Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), occurring in at least 1% in the TAA-AQ group and a greater incidence than with placebo were oropharyngeal pain, epistaxis, cough, upper respiratory infection and sinus headache (Table 4). AEs occurring in at least 1% in either TAA-AQ or placebo group are presented in Table 1 of Appendix 5.

In long-term clinical studies with adult and adolescent subjects, the most common events in Nasacort AQ treated subjects were nasopharyngitis, upper respiratory tract infection, and epistaxis. In one subject (open label TAA-AQ 220/110 mcg/day), with a history of previous nasal surgery, a 1 mm nasal septum perforation was noted at day 122 of the study. This case has been reported in the ‘Warnings and Precautions’ of the Nasacort AQ USPI (Appendix 3).

Table 4 - AEs in adults/adolescents (age 12 or greater) occurring in at least 1% in the TAA-AQ group and greater than Placebo (randomized placebo-controlled studies)

Preferred term n (%)	Placebo (N=955)		TAA-AQ (Total) (N=1389)	
Oropharyngeal pain	20	(2.1%)	33	(2.4%)
Epistaxis	8	(0.8%)	28	(2.0%)
Cough	13	(1.4%)	23	(1.7%)
Upper respiratory tract infection	5	(0.5%)	20	(1.4%)
Sinus headache	10	(1.0%)	16	(1.2%)

Source: XRG5029 / OTCNDA / ISS2012_02

Children

In children aged 2 through 11, AEs occurring in at least 1% in the TAA-AQ group and greater than in placebo were nasopharyngitis, upper respiratory tract infection, vomiting, abdominal pain, influenza, rash, viral infection, streptococcal pharyngitis, viral gastroenteritis, bronchitis, abdominal discomfort, arthropod bite and nasal discomfort (Table 5). AEs occurring in at least 1% in either TAA-AQ or placebo group are presented in Table 2 of Appendix 5.

Table 5 - AEs in children aged 2 through 11 occurring in at least 1% in the TAA-AQ group and greater than placebo (randomized placebo-controlled studies)

Preferred term n (%)	Placebo (N=624)		TAA-AQ (Total) (N=794)	
Nasopharyngitis	40	(6.4%)	62	(7.8%)
Upper respiratory tract infection	33	(5.3%)	44	(5.5%)
Vomiting	21	(3.4%)	37	(4.7%)
Abdominal pain upper	19	(3.0%)	33	(4.2%)
Influenza	19	(3.0%)	33	(4.2%)
Rash	9	(1.4%)	20	(2.5%)
Viral infection	7	(1.1%)	20	(2.5%)
Pharyngitis streptococcal	14	(2.2%)	18	(2.3%)
Gastroenteritis viral	7	(1.1%)	16	(2.0%)
Bronchitis	6	(1.0%)	12	(1.5%)
Abdominal discomfort	4	(0.6%)	9	(1.1%)
Arthropod bite	3	(0.5%)	8	(1.0%)
Nasal discomfort	6	(1.0%)	8	(1.0%)

Source: XRG5029 / OTCNDA / ISS2012_02

4.1.1.3 Serious Adverse Events

Adults and Adolescents

Eleven adults/adolescents experienced at least 1 SAE during treatment with TAA-AQ (Table 6). None of the SAEs were considered treatment related by the investigator. The only event reported in more than 1 subject was skull fracture that was reported in 2 adult subjects. One subject in a 6-month study developed sinusitis that required hospitalization. The AE started on study day 114 and the subject recovered by study day 120; TAA-AQ treatment was continued and the subject completed the 6-month study.

Table 6 - Serious Adverse Events in adult and adolescent subjects (All Clinical Studies)

Preferred term n (%)	TAA-AQ Total (N=4354)
Skull fracture	2 (<0.1%)
Asthma	1 (<0.1%)
Bronchitis	1 (<0.1%)
Cerebral hemorrhage	1 (<0.1%)
Coronary artery disease	1 (<0.1%)
Ligament sprain	1 (<0.1%)
Omental infarction	1 (<0.1%)
Papilloedema	1 (<0.1%)
Sinusitis	1 (<0.1%)
Testis cancer	1 (<0.1%)

Source: XRG5029 / OTCNDA / ISS2012

There were no SAEs with fatal outcome during clinical studies. Of note, one case of death due to metastatic gallbladder cancer was reported in a 50-year-old male patient after the study completion. This occurred 2 months after the last dose of the study medication (Nasacort AQ 110 mcg/day for 1 month) and was assessed by the investigator as unrelated to earlier Nasacort AQ study participation.

Appendix 6 provides a detailed listing of all SAEs observed across all clinical studies including those occurring in other treatment groups.

Children

Eleven children aged 2 through 11 experienced at least 1 SAE during treatment with TAA-AQ Table 7. None of SAEs were considered treatment related by the investigator. There were no SAEs with fatal outcome.

Two pediatric subjects had 2 SAEs each: adenoidal and tonsillar hypertrophy; and croup and pyrexia. One case of diabetic ketoacidosis (DKA) was reported in a 2 year old at day 90 of Nasacort AQ 110 mcg/day treatment when he developed new onset diabetes. One case of

suicidal ideation occurred secondary to a family court proceeding; the child was observed in an emergency room and released without treatment for suicidal ideation.

Table 7 - Serious Adverse Events in Children Aged 2 through 11 (All Clinical Studies)

Preferred term n (%)	TAA-AQ Total (N=1204)	
Adenoidal hypertrophy	1	(<0.1%)
Animal bite	1	(<0.1%)
Appendicitis	1	(<0.1%)
Asthma	1	(<0.1%)
Colitis ulcerative	1	(<0.1%)
Croup infectious	1	(<0.1%)
Diabetic ketoacidosis	1	(<0.1%)
Foreign body	1	(<0.1%)
Lymphadenitis	1	(<0.1%)
Meningitis aseptic	1	(<0.1%)
Pyrexia	1	(<0.1%)
Suicidal ideation	1	(<0.1%)
Tonsillar hypertrophy	1	(<0.1%)

Appendix 6 provides a detailed listing of all SAEs observed across all clinical studies including those occurring in other treatment groups.

4.1.2 Post-marketing Experience

A cumulative search of the Sanofi pharmacovigilance database was performed to identify all spontaneous postmarketing case reports through 29 February 2012 with TAA-AQ as a suspect drug. The case selection includes all spontaneous sources reported by healthcare providers (including healthcare professionals [HCP] and Health Authorities), as well as from consumers and published literature. The cumulative database search identified a total of 1,396 spontaneous cases reporting 2,643 adverse events. In the post-marketing safety tables, an individual post-marketing case may report more than one type of AE term. Additionally, an individual case may have more than one adverse event coded to the same AE term. This is applied to all safety data.

Reported events consistent with the known side effects of the product as described in the prescription label, have been considered as indication related, or analyzed as adverse events of special interest. Furthermore, in countries which have changed the availability of the product to nonprescription status, no change in AE reporting patterns have been detected.

4.1.2.1 Extent of Exposure

Based on Intercontinental Medical Statistics (IMS) Health data, from April 2000 through March 2012, more than 122 million TAA-AQ bottles were distributed globally with more than 50 million bottles sold in the US.

4.1.2.2 Adverse Events

Adults, Adolescents and Children

The most frequently reported AEs as a percentage of all reported AEs were drug ineffective, epistaxis, and headache (Table 8).

Table 8 - Post-marketing Adverse Events Reported in 1% or more Cases with Nasacort AQ (Adults, Adolescents and Children)

Preferred Term	No. (%) of AEs
Total adverse events	2643
Total individual case reports	1396
Drug ineffective	281 (10.6)
Epistaxis	134 (5.1)
Headache	120 (4.5)
Nasal discomfort	81 (3.1)
Dizziness	70 (2.6)
Nasal congestion	55 (2.1)
Dysgeusia	41 (1.6)
Oropharyngeal pain	41 (1.6)
Anosmia	37 (1.4)
Nausea	36 (1.4)
Rhinorrhoea	36 (1.4)
Cough	35 (1.3)
Hypersensitivity	34 (1.3)
Insomnia	33 (1.2)
Parosmia	32 (1.2)
Rash	29 (1.1)
Ageusia	26 (1.0)

Adolescents and Children

Of the total 2643 adverse events reported in all age groups, 136 AEs (5.1% of all events) occurred in sixty two (62) cases with pediatric patients (<18 years). It was noted that five (5) cases with a total of seven (7) AEs were reported in patients younger than 2 years of age, which is not an approved population for Nasacort AQ. These AEs were: psychomotor hyperactivity,

medication error, irritability, initial insomnia, decreased appetite, hypersensitivity, and cerebral ventricle dilatation (reported in utero and not present at birth).

In patients ages 2-<18 years the reported AEs by MedDRA PTs of ≥ 4 events were epistaxis, headache, hypersensitivity, irritability, blood cortisol decreased, ocular hyperaemia, and pruritus.

4.1.2.3 Serious Adverse Events

Adults, Adolescents and Children

No case with fatal outcome was reported. Ninety eight (98) spontaneous Nasacort AQ cases reported 201 serious adverse events (SAEs) and accounted for 7.6% of all AEs (Table 9). The most frequently reported SAEs (as a percentage of the total AEs) were cataract (0.5%), nasal septum perforation (0.5%), hypersensitivity (0.3%), and epistaxis (0.3%), which are labeled adverse drug reactions in the prescription label (USPI).

Table 9 - Post-marketing Serious Adverse Events Reported ≥ 4 events with Nasacort AQ (Adults, Adolescents and Children)

Preferred Term	No. (%*) of SAEs
Total AEs	2643
Total SAEs	201 (7.6)
Total case reports	98
Cataract	14 (0.5)
Nasal septum perforation	13 (0.5)
Hypersensitivity	8 (0.3)
Epistaxis	7 (0.3)
Dyspnoea	5 (0.2)
Anaphylactic reaction	5 (0.2)
Dizziness	4 (0.2)
Nausea	4 (0.2)
Decreased appetite	4 (0.2)
Weight decreased	4 (0.2)
Loss of consciousness	4 (0.2)
Blood cortisol decreased	4 (0.2)

*Note: Percentages of SAEs are calculated with the total number of events as the denominator (n= 2643)

Adolescents and Children

Ten pediatric cases reported 37 serious adverse events with the most frequently reported SAE of blood cortisol decreased. Two cases were identified for children aged 2 to <6 reporting the SAEs of cough and presyncope. Five cases were identified for children aged 6 to <12, 4 reports of blood cortisol decreased (group of 4 cases from one reporter) and one report of adenoidal hypertrophy. In the age group of 12 to <18, a total of 3 cases were identified reporting multiple

SAEs including angioedema, laryngeal edema, periorbital edema, pharyngitis, and nasal septum perforation.

4.2 ADVERSE EVENTS OF SPECIAL INTEREST

Sanofi has evaluated the following areas of special interest: local nasal AEs, ocular effects, immuno-suppression/ infection including infectious sinusitis, HPA axis suppression, growth effects, effects on bone metabolism, and effects on glucose metabolism.

These safety topics are reviewed below, incorporating data from clinical trials, published literature, and post-marketing experience. Data from the pediatric population are presented as relevant.

4.2.1 Localized Nasal Adverse Events

4.2.1.1 Summary

- In a clinical study of TAA-AQ in subjects with PAR, that incorporated nasal biopsies, there was no evidence of nasal mucosal atrophy over the 6 month treatment period.
- In clinical studies in adults and adolescents, nasal exams and cultures confirmed a single case of fungal infection in the nose.
- In clinical studies, epistaxis was reported in both TAA-AQ and placebo treated subjects. For adults and adolescents rates were higher in those treated with TAA-AQ; for children, rates were higher in those treated with placebo.
- One case of nasal septum perforation was reported in a clinical study in a subject (open label TAA-AQ 220/110 mcg/day) with a history of previous nasal surgery.
- The post-marketing database search identified epistaxis and nasal dryness as the most frequent local adverse events which presented 157 AEs. Seven out of 134 events of epistaxis were considered serious; none of these cases involved hospitalization. Ten cases reported nasal septum perforation.

4.2.1.2 Sanofi Sponsored Clinical Study

Use of TAA-AQ daily for 6 months, did not damage nasal mucosa as evaluated in Study 901, which included nasal mucosa biopsies. Subjects with PAR were randomized to treatment with TAA-AQ 220 mcg/day, beclomethasone dipropionate 400 mcg/day, or cetirizine 10 mg/day. There was no significant difference between TAA-AQ and other active comparators with regard to reduction of the nasal mucosa during the 6-month study period. Thus, no evidence of atrophy was observed during the study. TAA-AQ did not appear to cause any damage to the mucociliary apparatus, or retard mucociliary function during the study.

4.2.1.3 AEs in Clinical Studies

A retrospective search for AEs with potential effects related to local nasal effects was conducted across clinical studies in the integrated database with the following search criteria:

HLT: Nasal disorders NEC, Healing abnormal NEC or PT: Epistaxis.

In the placebo and active controlled studies of adults/adolescents, the rates of epistaxis were 2.6%, 4.6% and 0.8% in TAA-AQ, active control and placebo treated subjects, respectively. In placebo controlled studies of children aged 2-11, the rates of epistaxis were 5.8% and 6.3% in TAA-AQ and placebo treated children, respectively. One adult subject (open label TAA-AQ 220/110 mcg/day), with a history of previous nasal surgery, was found to have 1 mm nasal septum perforation noted at day 122 of the study.

Use of TAA-AQ rarely results in local nasal fungal infections. The clinical studies supporting the approval of TAA-AQ in adults/adolescents incorporated specific evaluations of the nose, looking for potential fungal infections. In studies conducted in Europe, nasal swab cultures for fungus were routinely collected irrespective of findings on nasal inspection. From those studies similar results for Candida growth were reported from TAA-AQ and placebo treated subjects and none were considered clinically relevant. In US studies cultures were performed only when fungal infection was suspected by exam. A single TAA-AQ treated subject had a suspected fungal infection in the nose with a confirmed laboratory culture.

4.2.1.4 Findings in Literature

Ozturk (17) studied 34 children with AR or AR and asthma to investigate the effect of TAA-AQ 220 mcg/day for 4 weeks on bronchial hyper-responsiveness and nasal patency. One patient reported epistaxis during the study but did not discontinue treatment.

4.2.1.5 Findings from post-marketing

A search of the post-marketing safety database identified 157 cases reporting 199 AEs of local nasal events with TAA-AQ. The most frequent AEs were epistaxis and nasal dryness which presented 157 AEs. Seven out of 134 events of epistaxis were considered serious, none of these cases involved hospitalization.

Nine cases of nasal septum perforation (coded as 13 AEs of nasal septum perforation), along with one recent case (total 10 cases) have been reported to post-marketing safety. Of these 10 cases, 5 were from HCPs. Other types of localized nasal AEs were relatively few and included mostly non-serious cases with insufficient information for an adequate medical evaluation. Some of them may present signs of disease target, such as nasal polyps. Epistaxis and nasal septum perforation are listed adverse drug reactions in the Nasacort AQ USPI. From the review of these post-marketing events, no new safety concerns were identified.

4.2.2 Ocular Effects

4.2.2.1 Summary

- In clinical studies, there were no adverse event reports of increased intraocular pressure, glaucoma or cataracts. There were no specialized studies evaluating intraocular pressure, glaucoma or cataracts.
- There were no relevant publications on ocular safety and treatment with TAA-AQ.
- The post-marketing database search identified 41 cases, including 17 cataract, 20 intraocular pressure increased/ocular hypertension, and 6 glaucoma/angle closure glaucoma.

4.2.2.2 AEs in Clinical Studies

A retrospective search for AEs with potential effects related to ocular safety was conducted across clinical studies in the integrated database with the following search criteria with standard MedDRA query (SMQ):

- SMQ: Glaucoma (broad + narrow), SMQ: Lens disorders (Narrow).

No cases of increased intraocular pressure, glaucoma or cataracts were identified in the retrospective search, in the adult/adolescent subjects or the pediatric subjects.

4.2.2.3 Findings in Literature

No publications have been identified that address the topic of ocular effects including glaucoma and cataracts with TAA-AQ.

4.2.2.4 Findings from post-marketing

A search of the post-marketing safety database focusing on the events of cataract, intraocular pressure increase, glaucoma, ocular hypertension, and angle closure glaucoma following the comprehensive SMQ exploration, revealed a total of 41 cases. They included 14 HCP cases, and 27 consumer reports. They represented 2.9 % (41/1396) of total cases for Nasacort AQ. The 41 cases reported a total 17 for cataract, 20 for intraocular pressure increased including ocular hypertension, and 6 for glaucoma including angle closure glaucoma. Two cases reported more than one ocular event of interest. These ocular events represented 1.8% (48/2643) of total events for Nasacort AQ, with cataracts 0.8%, intraocular pressure increased 0.7%, glaucoma 0.2%, ocular hypertension <0.1%, and open angular glaucoma <0.1%. It is known that oral corticosteroids are associated with posterior subcapsular cataracts and can lead to increases in intraocular pressure and glaucoma. Glaucoma and cataract are common conditions, particularly in the age 40 and over population. No case of increase intraocular pressure, glaucoma and cataracts in children were reported to Sanofi.

In addition, one case of cataract was reported directly to the FDA and not to Sanofi and is presented here: An 11-year-old female received Nasacort AQ for allergic rhinitis for 2 years

followed by co-suspect Nasonex (intranasal mometasone furoate) for 4 years. Concomitant medications include Zyrtec, and Claritin. Patient received treatment drugs only during the allergy season from spring to frost. After two years of treatment with Nasacort AQ then 4 years of treatment with Nasonex the patient was diagnosed with posterior subcapsular cataracts.

4.2.3 Immunosuppresion/Infection including Infectious Sinusitis

4.2.3.1 Summary

- In clinical studies there were no adverse events of immunosuppression or opportunistic infection.
- In controlled studies with adults/adolescents, sinusitis was reported in 1.2% and 0.8% of TAA-AQ and placebo treated subjects, respectively. In placebo-controlled studies in children 2-11 years of age, the rates were 3.1% and 4.3% in TAA-AQ and placebo treated subjects, respectively.
- In a publication it was reported that treatment with TAA-AQ for 2 months did not increase the prevalence of nasal carriage of *Staphylococcus aureus.*
- The post-marketing safety database search identified 74 cases of infections. Infectious sinusitis was the most frequently reported. There were no cases of immunosuppression or opportunistic infection.
- Measles, tuberculosis, and chicken pox, diseases which are known to occur or worsen with oral corticosteroids, have not been reported with the use of TAA-AQ.

4.2.3.2 AEs in Clinical Studies

A retrospective search for AEs with potential effects related to immunosuppression was conducted in the clinical studies integrated database using the PT of interest “Opportunistic infections” in the system organ class (SOC) “Infections and infestations” and PTs including “Immunosuppression” in the SOC “Immune system disorders”. No adverse events of interest were found.

In addition, a retrospective search for AEs with potential effects related to sinusitis was conducted in the clinical development integrated database using the following broad search criteria:

- PTs under “Infections and infestations” SOC: Sinusitis, Acute sinusitis, Bacterial rhinitis, Chronic sinusitis, Fungal rhinitis, Nasal candidiasis, Oral candidiasis, Oral fungal infection, Oro-pharyngeal aspergillosis, Oropharyngeal candidiasis, Oropharyngitis fungal, Sinusitis, Sinusitis aspergillus, Sinusitis bacterial, Sinusitis fungal, Viral sinusitis.

In the controlled studies in adult/adolescent subjects, the incidence of AEs related to sinusitis was low in all treatment groups. Sinusitis was reported in 1.2% (28/2387), 0.8% (8/955) and 0.5% (6/1315) of subjects in TAA-AQ, placebo and active comparator groups, respectively. A review of events in the TAA-AQ treated subjects suggested that only 8/28 sinusitis events were

infectious in etiology. One 23 year old female TAA-AQ subject in a 6-month study developed sinusitis that required hospitalization. The AE started on study day 114, and the subject recovered by study day 120. The subject recovered without sequelae, continued TAA-AQ treatment and completed the 6 month study. In placebo-controlled studies of children aged 2-11, 3.1% (25/794) and 4.3% (27/624) subjects were reported with sinusitis in the TAA-AQ and placebo groups, respectively.

Sinusitis events were reported at similar rates in TAA-AQ and placebo treated subjects. The majority of these events in active or placebo subjects do not point to an infectious etiology. No safety concerns for infectious sinusitis were observed in the adult/adolescent subjects or the pediatric subjects.

4.2.3.3 Findings in Literature

Two publications have been identified that are relevant to the topic of infections, including infectious sinusitis with TAA-AQ.

Kang et al (18), investigated the use of TAA administered for 2 months as TAA-AQ 220 mcg daily (n=18) or aqueous TAA (40 mg/vial) soaked pads changed weekly (N=14) for prevention of nasal polyps after endoscopic sinus surgery. The TAA soaked pad was more effective for this purpose. One patient in each group developed purulent discharge which was completely controlled with one week of oral antibiotics. Yilmaz et al (19) reported that use of TAA-AQ 220 mcg/day for 2 months treatment for AR did not increase the prevalence of nasal carriage of *Staphylococcus aureus,* a state which has been associated with other infectious complications.

4.2.3.4 Findings from post-marketing

Adverse events of infections were reviewed in the postmarketing safety database search and defined as PTs coded to the MedDRA System Organ Class (SOC) of Infections and infestations. In addition, PT of interest ‘Opportunistic infections’ included in this SOC and PTs including ‘Immunosuppression’ in the SOC ‘Immune system disorders’ were also searched.

A total of 74 cases were identified. Among these, 10 involved serious infection (3 pneumonia, 1 rhinitis, 1 fungal sinusitis, 1 histoplasmosis, 1 endocarditis, 1 fungal infection, 1 pharyngitis, and 1 pharyngitis/rhinitis). Sinusitis was the most frequently reported AE. No cases of ‘Opportunistic infections’ or ‘Immunosuppression’ were identified.

4.2.4 HPA Axis Suppression

4.2.4.1 Summary

- Four specialized studies of HPA axis reserve and basal function showed a low potential for HPA axis suppression with TAA-AQ in adults or children.

- Several independent publications report evaluations of the effects of TAA-AQ on the HPA axis. No effects on the HPA axis were identified with intranasal administered TAA-AQ.

- The post-marketing safety database search identified 5 cases of potential adrenal cortical effects reported by HCP and 1 case reported by a consumer with insufficient information for a full assessment. All 5 cases reported by HCP were confounded by concomitant steroid treatment.

4.2.4.2 Sanofi Sponsored Clinical Studies to Evaluate Potential HPA Axis Suppression

Four clinical studies were conducted to address potential effects on HPA axis suppression, three of which are reflected in the current USPI. One post-marketing commitment study, TRICA_L_04286 is currently under review by the FDA.

Study 102

In Study RG5029Y-102, the HPA axis function during treatment with TAA-AQ (220 or 440 mcg/day) was compared to placebo and to 10 mg/day prednisone capsules administered daily for 42 days. Subjects aged 19 to 50 with AR were enrolled.

At baseline and Week 6 following treatment with study medication, plasma cortisol levels collected six hours post 250 mcg cosyntropin stimulation were compared between treatment groups. HPA axis suppression was defined as a plasma cortisol level below18 mcg/dL, after cosyntropin stimulation at Week 6 post treatment. No patients exhibited clinical HPA axis suppression per the pre-specified criterion. The treatment differences in change from baseline of post-stimulation plasma cortisol (mcg/dL) with placebo for TAA-AQ 440 mcg/day, TAA-AQ 220 mcg/day and prednisone were -1.81 (95% CI: -8.91, 5.29), 2.93 (95% CI: -4.17, 10.03) and -18.25 (95% CI: -25.35, -11.15), respectively. There were no statistically significant effects on HPA function with TAA-AQ 220 mcg/day, or with TAA-AQ 440 mcg/day (twice the maximum daily dose per label) compared to placebo.

Study 125

In Study RG5029Y-125, potential HPA axis suppression was evaluated in 6 to 12 year old subjects exposed to placebo, TAA-AQ 220 mcg and TAA-AQ 440 mcg. To evaluate HPA function, the plasma cortisol levels post 250 mcg cosyntropin stimulation was compared at baseline and Week 6 following treatment with study medication. At one hour post cosyntropin stimulation, no patients exhibited clinical HPA axis suppression per pre-specified criteria. The treatment differences in change from baseline of post-stimulation plasma cortisol (mcg/dL) with placebo for TAA-AQ 440 mcg/day and TAA-AQ 220 mcg/day were 1.50 (95% CI: -0.54, 3.54) and 0.37 (95% CI: -1.64, 2.38), respectively. There was no statistically significant effect on HPA function among subjects treated with TAA-AQ (TAA-AQ 220 mcg or TAA-AQ 440 mcg) versus subjects treated with placebo.

Study 3502

In Study 3502 the effect of TAA-AQ 110 mcg administered daily on the HPA axis in a subset of children 2 to 5 years of age was evaluated. In the double-blind 4 week treatment period, study drug was TAA-AQ 110 mcg/day or placebo. The double blind period was followed by a 6 month open label treatment in which all subjects received TAA-AQ 110 mcg/day. Low dose (1 mcg) cosyntropin stimulation tests were performed to assess HPA axis function, at screening baseline, 4 weeks and 6 months. The treatment difference in change from baseline of serum

cortisol post-stimulation change (mcg/dL) with placebo for TAA-AQ 110 mcg/day was -1.07 (95% CI: -4.97, 2.83). There was no statistically significant difference between the placebo and the TAA-AQ groups (p=0.5838) in cortisol responses at the end of double-blind treatment period and no statistically significant differences at the end of the open-label treatment period compared to screening. Based on these results, there appears to be no consistent suppressive effect on the HPA axis. However, some subjects did not show the pre-specified increase in cortisol levels or did not reach the pre-specified level following cosyntropin stimulation. Therefore, a possible treatment effect on children ages 2-5 cannot be ruled out.

Study TRICA_L_04286

Study TRICA_L_04286, was initiated to evaluate the effect of a 6-week treatment with TAA-AQ (110 mcg or 220 mcg based on age) versus placebo on basal HPA axis function, as measured by serum cortisol area-under-the-curve, AUC (0-24 hr) in children aged 2-11 with AR. Assessment of 24 hr cortisol production (without a stimulus) is a sensitive measure of HPA axis function. In the per-protocol population analysis of the change from baseline in serum cortisol AUC (0-24 hr), the difference between TAA-AQ and placebo in change from baseline of AUC (0-24 hr) was -4.2 (95% CI: -14.7, 6.4) mcg·hr/dL, and the ratio of TAA-AQ to placebo was 0.966 (95% CI: 0.892, 1.045). The geometric mean changes from baseline (ratio) were 0.898 for the TAA-AQ group and 0.938 for the placebo group. The results for the primary endpoint in the intend-to-treat (ITT) population were consistent with those observed in the PP population, as were results for analyses by age, and TAA-AQ dose. The mean serum cortisol levels at the nominal sampling time points are presented in Figure 1 of Appendix 5.

Taken daily for 6 weeks, TAA-AQ in children aged 2-11, did not suppress the HPA axis as measured by 24 hour serum cortisol AUC.

4.2.4.3 AEs in Clinical Studies

A retrospective search for AEs with potential effects related to HPA axis suppression was performed on clinical studies in the integrated database with the following search criteria:

- HLT: Adrenal cortical hypofunction, Adrenal cortical hyperfunction, Adrenal medulla disorders, Immunodeficiency disorders NEC, Adrenal cortex tests.

Based on this search, no subjects with AEs from adult/adolescent studies were identified. In studies of children aged 2-5, 3 TAA-AQ and 2 placebo treated subjects had study specific cortisol measures that were considered laboratory adverse events. All of the events were considered mild in intensity and were without corresponding clinical adverse events.

4.2.4.4 Findings in Literature

Several publications report evaluations of the effects of TAA-AQ on the HPA axis. Reported assessments include measurements of basal (serum, salivary or urinary cortisol measures) and dynamic changes (cortisol measures in response to Adrenocorticotropic Hormone (ACTH) stimulation) to assess HPA Axis function.

Studies published by Bachert et al (20) and Kang et al (18) reported no significant differences on HPA axis effects by using urinary or serum cortisol assessments after TAA-AQ treatment. Robb et al (21) reported no detectable HPA axis effects by assessing overnight urinary cortisol corrected for creatinine, and by plasma cortisol following treatment with TAA-AQ 220 mcg/day and mometasone furoate 200 mcg/d, in a crossover study. Ober et al (22) and Skoner et al (23) reported that mean salivary cortisol was not significantly changed after a one year treatment with TAA-AQ.

Wilson and colleagues conducted three separate crossover studies evaluating the effects of intranasal steroids on basal HPA axis function. In one study (24), they evaluated the effects of inhaled steroids with and without concomitant intranasal steroids. They reported that inhaled fluticasone propionate and inhaled triamcinolone acetonide produced significant adrenal suppression compared with placebo. In the case of inhaled triamcinolone acetonide, addition of intranasal TAA-AQ did not produce significant further suppression of mean values of 24 hour and fractionated serum cortisol levels and urinary cortisol/creatinine excretion. In another study, Wilson et al (25) reported that suppression of overnight urinary cortisol occurred significantly with intranasal fluticasone propionate (43%) and non-significantly with TAA-AQ (23%) and intranasal beclomethasone dipropionate (21%). In a third study (26), they compared the bioactivity of 5 days of administration of the intranasal steroids, mometasone furoate 200 mcg/d, TAA-AQ 220 mcg/d, budesonide 200 mcg/day with placebo. None of these produced significant systemic suppression of adrenal function as assessed by 24 hour and fractionated urinary and plasma cortisol levels.

4.2.4.5 Findings from Post-marketing

Six cases related to HPA axis effects were identified with TAA-AQ: 4 serious and 1 non-serious HCP cases and 1 non-serious consumer case. Four events of blood cortisol decreased were reported by the same physician as a group report, and were confounded by the concomitant use of inhaled fluticasone propionate. One other non-serious HCP case was reported as hyperadrenocorticism and had concomitant use of intranasal fluticasone propionate. The remaining 1 non-serious case of blood cortisol increased was a consumer report.

In addition, one case of adrenal suppression was reported directly to the FDA and not to Sanofi and is presented here: A 12-year-old male received Nasacort AQ for asthma and allergies. Concomitant medications include Flovent, albuterol, Singulair, loratadine and a 5 day course of prednisone (dose not reported). After a prolonged viral illness with asthma that did not improve despite 5 day prednisone the patient was seen by an immunologist. The reported events are an 8AM cortisol = 2.5 mcg/dl and poor growth. Treatment with Nasacort AQ was discontinued. The report does not indicate if therapy of concomitant medications was changed. The event had not resolved at the time of reporting.

4.2.5 Effects on Growth

4.2.5.1 Summary

- In a study in prepubescent children, a 0.45 cm reduction in 1 year growth rate in the TAA-AQ treatment group was observed and was statistically significant when compared to placebo. Following TAA-AQ discontinuation after 1 year, growth velocity

approximated baseline velocity.

- There were no AEs in clinical studies reported as an adverse effect on growth.
- In publications no significant effects of TAA-AQ on growth were identified.
- The post-marketing safety database search identified 2 non-serious cases reporting growth retardation with TAA-AQ in children. Neither case provided sufficient information for a full assessment.

4.2.5.2 Sanofi Sponsored Clinical Studies to Evaluate Pediatric Growth

Two clinical studies (short term knemometry and one year growth velocity) conducted by Sanofi specifically examined the effect of TAA-AQ on pediatric growth and are discussed below. Additionally, efficacy/safety study 3502 in children aged 2-5 with PAR measured height along with other assessments. The distribution for age of the height percentiles was maintained over the course of the 6 month study for these children treated with TAA-AQ.

Study 315 evaluated the effect of TAA-AQ on lower leg length by knemometry in children 4 to 10 years of age. TAA-AQ dosed at 110 mcg/day and 220 mcg/day were compared with placebo and the active comparator - Flonase Nasal Spray (200 mcg/day), in a randomized, 4-way cross-over study over 14 weeks (2 weeks treatment with 2 weeks wash-outs). In this short-term study, TAA-AQ at doses of 110 mcg or 220 mcg once daily did not have a clinically significant effect as defined in the protocol on lower leg growth. The treatment differences in lower leg growth velocity with placebo for TAA-AQ 110 mcg/day, TAA-AQ 220 mcg/day and Flonase Nasal Spray (200 mcg/day) were -0.14 (95% CI: -0.30, 0.02), -0.17 (95% CI: -0.33, -0.01) and -0.13 (95% CI: -0.29, 0.04) mm/week, respectively.

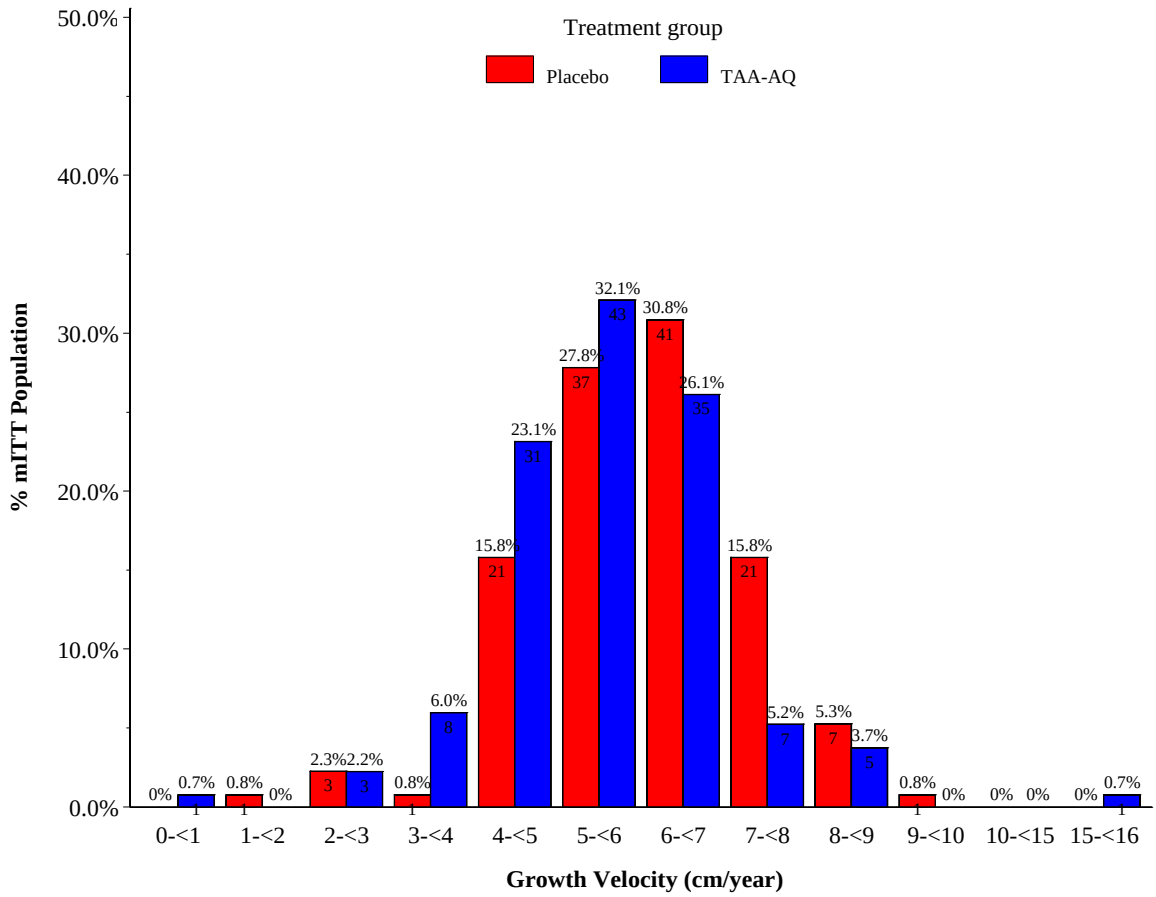
Study 3503, a post-marketing commitment study characterized the effect of growth in children 3 to 9 years of age with PAR and was conducted in accordance with FDA guidance (27). This study is currently under review by the FDA. Prepubertal children aged 3-9 were studied because growth is relatively linear during this period. Until age 3, nutrition significantly affects growth and just prior to and throughout puberty growth is more variable and the sex hormones are principal drivers to growth. The study assessed the difference in growth velocity (rate of growth in cm/year) in children treated with TAA-AQ versus placebo during a 12 month double-blind treatment period. The pre-specified primary endpoint was the growth velocity during treatment period (12 months). The growth over the first 4 months and growth in the two month follow-up after discontinuation of study medication were among the pre-specified secondary endpoints. Growth was assessed using stadiometry for both screening period of 4-6 months prior to randomization to double blind treatment of 12 months and post-treatment follow-up period of 2 months. Sites were trained on the use of specially installed wall-mounted stadiometers for height measurements. The growth velocity of each patient was calculated as the slope of a linear regression of the patient's height and age.

The primary analysis population (n=267) was well balanced between the two treatment groups, by age and gender. The growth velocity during the double-blind treatment period was lower in the TAA-AQ group (5.65(SE: 0.122) cm/year) than in the placebo group (6.09 (SE: 0.122)

cm/year). The difference in LS mean growth velocity (TAA-AQ minus placebo) was -0.45 cm/year (95% CI: -0.78, -0.11) and was statistically significant (p=0.0096). The mean height changes from baseline in the mITT population by visit are presented in Figure 2 of Appendix 5. In the 2 month follow-up period after end of the treatment, the observed mean growth velocity (6.59 cm/year) in the TAA-AQ group had increased nearly to the magnitude that was observed during the screening/baseline period (6.70 cm/year). In the placebo group, the observed mean growth velocity decreased slightly in the follow-up period (5.89 cm/year in the follow-up period compared to 6.06 cm/year during the screening/baseline period).

One year growth rates were examined in each group to evaluate the potential for marked decreases in growth with TAA-AQ. To examine the data for outliers in growth velocity, **Figure 5** displays the distributions of growth velocity for subjects in the placebo and TAA-AQ treatment groups. Results in both treatment groups are consistent with normal growth velocity distributions. The distribution of TAA-AQ group is slightly shifted to the left (lower velocities) compared to the distribution for the placebo group, but without any evidence of marked abnormality (outliers) in growth suppression.

Figure 5 - Distribution of Growth Velocity (cm/year) for TAA-AQ and Placebo



Source: PGM=DEVOPS/XRG5029/UMA03503/CSR/REPORT/PGM/gv_bar_m_g.sas OUT=REPORT/OUTPUT/gv_bar2_m_g_x.rtf

4.2.5.3 AEs in Clinical Studies

A retrospective search for AEs with potential effects related to growth was performed on clinical studies in the integrated database with the following search criteria:

- PT: Growth retardation, Bone development abnormal.

Based on this search no AEs affecting growth was observed in the adult/adolescent subjects or the pediatric subjects.

4.2.5.4 Findings in Literature

Schaffner (28) and Skoner (29) (30) reported on an investigator initiated study US1_631; results for years 1, 2, 3 and 4 of TAA-AQ treatment showed no significant effect of TAA-AQ on growth.

4.2.5.5 Findings from post-marketing

A total of 2 non-serious cases reported growth retardation with TAA-AQ in children: one involved an 11-year-old boy (HCP case) and one involved an 8-year-old girl (consumer case). Neither case provided sufficient information for a full assessment.

4.2.6 Effects on Bone Metabolism

4.2.6.1 Summary

- AEs related to bone metabolism were not reported in clinical studies.
- Two cases of aseptic necrosis were reported in the literature in patients treated with TAA-AQ; both patients had additional steroid use.
- The post-marketing database search identified 4 cases: 2 of bone loss, 1 of bone formation decreased, and 1 of osteopenia.

4.2.6.2 AEs in Clinical Studies

A retrospective search for AEs with potential effects related to bone metabolism was performed on clinical studies in the integrated database with the following search criteria:

- HLT: Bone disorders NEC, Bone metabolism disorders, Biochemical markers of bone metabolism, metabolic bone disorders.

No AEs related to bone metabolism were reported in the adult/adolescent or the pediatric subjects.

4.2.6.3 Findings in Literature

Studies on serum osteocalcin, a marker of bone metabolism, as a secondary measure (21) (31) (32) have reported that serum osteocalcin remained unchanged in TAA-AQ treatment groups from baseline measures.

Two cases of osteonecrosis (aseptic necrosis) of the femoral head are identified in the literature by Karkoulis (33) and Mistlin (34). One patient took TAA-AQ 220 mcg QID for one year and used as needed beclomethasone dipropionate nasal spray along with 4 sprays of TAA-AQ four times daily, besides having a history of previous QID dexamethasone nasal spray use for chronic rhinosinusitis (34). The other patient, with a history of asthma and nasal polyposis, took TAA-AQ BID for 5 years, inhaled fluticasone propionate 1000 mcg/day for 3 years and methylprednisolone 40 mg BID for an unknown duration (33). In each of the two cases of aseptic necrosis, the individual had a history of prior corticosteroid use and used excessive daily doses of TAA-AQ.

The two published cases involve long term use of TAA-AQ at excessive frequencies and are complicated by other corticosteroid use. Contributions of TAA-AQ use to the two reported cases cannot be excluded since corticosteroid use is a recognized risk factor for this condition.

4.2.6.4 Findings from post-marketing

Four cases described effects on bone metabolism with TAA-AQ. They included 2 serious and 2 non-serious cases. One serious HCP case described the event of severe bone loss around one tooth in a 70-year-old female patient after 6 days of use with TAA-AQ to treat chronic cough. The case can be alternatively explained by the patient's advanced age and the fact that periodontal disease with bone loss requires more time for evolution, despite limited information. The remaining 3 consumer reports were reviewed and revealed no significant safety findings.

4.2.7 Effects on Glucose Metabolism

4.2.7.1 Summary

- No AEs were reported in clinical studies that affirms an impact of TAA-AQ on glucose metabolism. One case of diabetic ketoacidosis was reported in a child with new onset diabetes.
- There were no publications that evaluated the effect of TAA-AQ on glucose metabolism.
- In the post-marketing safety database search, 9 cases of abnormalities in glucose metabolism were reported but the events are common in the general population and there was no specific information that link event occurrence to TAA-AQ treatment.

4.2.7.2 AEs in Clinical Studies

A retrospective search for AEs with potential effects related to glucose metabolism on clinical studies in the integrated database with the following search criteria:

- SMQ: Hyperglycemia/new onset diabetes mellitus (broad + narrow).

In clinical studies, one subject, a two-year old white male, on TAA-AQ 110 mcg/day presented with diabetic ketoacidosis which was considered secondary to new onset diabetes mellitus. The diabetic ketoacidosis was reported as an SAE. The subject was hospitalized for three days, recovered from the DKA event but was discontinued from the study. The investigator considered it unrelated to study treatment.

No other events relevant to glucose metabolism were reported in clinical studies of adults/adolescents or children.

4.2.7.3 Findings in Literature

No publications have been identified that address the topic of glucose metabolism with TAA-AQ.

4.2.7.4 Findings from post-marketing

A total of 9 glucose metabolism related cases were identified. Five of the HCP cases, including blood glucose increased (4 cases), and one case with both glycosylated hemoglobin increased and insulin resistance, provided insufficient information to support a definitive causal assessment. The remaining 4 consumer reports were reviewed and revealed no new significant safety findings.

4.3 REVIEW OF FDA AERS AND WHO VIGIBASE PHARMCOVIGILANCE DATABASES

An analysis of safety data from external spontaneous reporting systems using data mining methods was conducted to identify any safety signal, warranting further investigation. Disproportionality analysis was performed using Empirica Signal™ to evaluate reports recorded in the FDA AERS database. The disproportionality analysis in the FDA AERS database using Multi-Item Gamma Poisson Shrinker (MGPS) method with signal score of EB05 >= 2, for events at MedDRA PT, HLT and SMQ narrow or algorithmic levels, identified no new signals warranting further investigation in the period when TAA-AQ formulation has been available on the US market. Most events identified as signal of disproportionate reporting in the FDA AERS database from 1996 are either labeled in the current USPI, or considered as indication related, or have been analyzed as AEs of Special Interest (AESI). Disproportionality analysis of non-US reports in the WHO VigiBase also identified no new safety signals in the period when TAA-AQ formulation has been available on the market or in the other time periods considered.

5 THE OTC DEVELOPMENT PROGRAM

5.1 OVERVIEW OF OTC DEVELOPMENT PROGRAM

The major goal of the development program for the OTC switch of Nasacort AQ from prescription to OTC status was to develop a label that consumers could understand, so that it could guide their use of the medication without the intervention of a physician. The proposed OTC label for Nasacort AQ was developed based on the prescription label for Nasacort AQ and the labels for existing OTC products indicated for treatment of AR, and with input from FDA.

The proposed OTC labeling for Nasacort AQ consists of two parts: the Drug Facts Label (DFL) and a Consumer Information Leaflet (CIL). The DFL, which is mandated for all OTC medications, appears on the outer carton and on the immediate container of the product (i.e., the bottle). It communicates the indication, directions for use, and warnings. Its format is highly standardized and regulated (Code of Federal Regulations § 201.66), and includes specified sections for Active ingredients, Uses (the indication), Directions (how to dose the product), and Warnings (including *Do not use* for absolute contraindications, *Ask a doctor before use* for relative contraindications, *Stop use and ask a doctor* for identifying signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product, and *When using this product* for identifying side effects that may be experienced.) The proposed DFL for Nasacort AQ is included in Appendix 1.

The proposed labeling for Nasacort AQ also includes a CIL (see Appendix 2), which will be enclosed in the OTC package. The CIL includes text and illustrations to explain how to administer the spray, how to prime the spray bottle, and how to clean the nozzle should it become clogged. The proposed CIL also repeats the product directions.

Both the DFL and the CIL were tested for consumer comprehension, as described below. FDA advised that AR is already an established OTC indication, that consumers already successfully self-treat AR with nasal sprays, and that the proposed OTC label for Nasacort AQ largely consisted of elements already present for marketed OTC products. Accordingly, FDA recommended that label comprehension and human factors studies should focus on the use of the Nasacort pump, which is a more unique aspect of consumer directions. Furthermore, self-selection and actual consumer use studies were not deemed necessary, given the favorable experience with other OTC products and labels, including those for OTC AR products.

Based on the FDA input, the label comprehension study was designed to evaluate as its primary endpoint the unique aspects of the Nasacort AQ product, focusing on consumer understanding of the need to prepare the pump for first use (priming) as the primary communication objective for testing of both the DFL and CIL. The label comprehension studies were conducted in accordance with FDA Guidance for Industry entitled “Label Comprehension Studies for Nonprescription Drug Products” (7). Per FDA’s guidance, the studies designated preparation of the pump for first use as the primary end-point, and the sample included approximately 30% low-literacy individuals. In addition to testing these primary end-points, the full range of label communications, including the indication, dosing frequency, maximum number of sprays, warnings, and other label statements were tested, and results are reported below. Language to communicate to consumers the potential for reduction in growth velocity in children was

subsequently developed, and was tested in separate cohorts of consumers, in the context of the full DFL. The DFL, CIL, and growth statements each underwent iterative development through two rounds or phases of testing, using results and feedback from the first phase (referred to as Phase 1) to revise the labeling, with revisions then tested in the second phase. The labeling proposed reflects the language tested in the second phase (referred to as Phase 2).

A human factors study evaluated consumer's ability to carry out tasks related to maintenance of the spray bottle. Per FDA recommendations, the study focused on priming and re-priming the bottle and cleaning the nozzle.

The findings from these studies are described below.

5.2 FINDINGS IN LABELING COMPREHENSION STUDIES

5.2.1 Summary of Findings

- The label comprehension studies of the DFL and CIL separately enrolled participants in two phases of study. The first phases led to modifications in the DFL and CIL that were retested in Phase 2. Success in testing the primary communication objectives was pre-specified as a lower 95% CI of at least 80% comprehension.

- The primary communication objective for the DFL was defined as understanding the need to get a new bottle of Nasacort ready (primed) before first use. In the Phase 2 study sample of 325 subjects, 86.8% of subjects (95% CI: 82.6%, 90.3%) understood the communication meeting the pre-specified definition for success.

- The primary communication objective for the CIL was defined as understanding the need to prime a bottle before first use. In the Phase 2 study sample of 411 subjects, 88.6% of subjects (95% CI: 85.1%, 91.5%) understood the communication meeting the pre-specified definition for success.

- All secondary communication objectives for both the DFL and the CIL were successfully communicated.

5.2.2 Study Design

5.2.2.1 Methodology

Study 2012002 was conducted at multiple retail centers across the US to test key messages included in the DFL and CIL regarding use of the Nasacort pump and other communications. The study used an iterative study design in which initial testing in Phase 1 led to modifications to the DFL and CIL. The modified statements were tested in Phase 2. Changes were made to questionnaire wording, where Phase 1 consumer responses indicated a question was unclear.

The primary objectives in testing the DFL and CIL focused on consumer understanding of the following label directions:

- DFL: Get a new bottle ready (primed) before first use.

- CIL: A new bottle of Nasacort must be primed before first use.

The study was conducted in accordance with FDA Guidance for Industry entitled "Label Comprehension Studies for Nonprescription Drug Products." That Guidance requires sponsors to pre-specify a target for the percentage of consumers who understand the label elements designated as primary end-points. The target comprehension level is expected to reflect the clinical consequences of failing to comprehend or follow the particular instruction. In these studies, per FDA's advice, understanding the need to prime the pump was designated as the primary end-point for both the DFL and CIL.

The pre-specified success for the primary end-points was defined as at least an 80% comprehension by study participants across the entire sample. By protocol, the lower 95% confidence limit must equal or exceed 80% in the sample as a whole to define successful communication of the primary end-point.

Recruitment targets were set to ensure that:

- about half of the participants were male;
- about 30% of the sample had low health literacy (defined by REALM scores);
- 16 and 17 year olds were represented in the study.

Although the FDA Guidance for Label Comprehension Studies only requires setting and testing pre-specified success criteria only for the primary endpoint, the criteria were applied for all endpoints. Secondary communication objectives for the DFL were required to reach 80% comprehension and concerned consumer understanding of the following directions:

- ask a doctor before use if you have had recent nasal ulcers, nasal surgery or nasal injury that has not healed.
- ask a doctor before use if you are using an asthma medicine or a prescription steroid medicine.
- ask a doctor before use if you have or had glaucoma or cataracts.
- stop use and ask a doctor if you have an allergic reaction, such as a rash, problems swallowing or breathing, swelling of our lips, face or tongue. Seek medical help right away;
- stop use and ask a doctor if you have, or come into contact with someone who has chickenpox, measles, or tuberculosis.

Secondary communication objectives for the CIL were required to reach 80% comprehension and concerned consumer understanding of the following directions:

- if the pump does not spray properly, the nozzle may be blocked: clean the nozzle AND never try to unblock nozzle with a pin or any object (two separate messages);

- if Nasacort has not been used for more than 2 weeks, prime bottle again following the previous steps used to prime a new bottle.

The retail sites (large shopping malls) at which participants were recruited were selected from diverse geographic areas of the US. Recruiters from the research facility, who were trained to use the screening instrument, approached and screened potential participants in a consumer traffic area of the shopping center immediately around the research facility.

One-on-one interviews were conducted with participants in which participants were asked questions from a standardized questionnaire to assess each communication objective and message. The questionnaire primarily consisted of open-ended questions, including direct questions and hypothetical scenarios. No multiple-choice questions were used. These responses were subsequently scored as correct or acceptable (with both counted towards comprehension statistics), or incorrect. At the conclusion of the label comprehension interview, incorrect responses were reviewed with participants to determine where confusion occurred and why incorrect responses were given. These debriefing responses were not used to mitigate incorrect responses.

For consumer assessment of the DFL, participants were given a three-dimensional color carton simulating the outer box as it would appear on a store shelf in the OTC environment. The carton contained the CIL and an empty product bottle. For CIL assessment, participants received an unfolded CIL, which was approximately the same size as that proposed for the commercial OTC product. Participants evaluating the CIL also had access to the carton with the DFL, but the DFL was not handed to them nor were they asked to read it.

Literacy was measured using Rapid Estimate of Adult Literacy in Medicine (REALM) for participants 18 years of age and older and Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) for participants 16-17. A score of 60 or less defined the low literacy group. Recruitment aimed to achieve a sample that included approximately 30% of participants classified as low literacy.

5.2.2.2 Exclusion Criteria

Participants were excluded if they met any of the following criteria:

- younger than 16 years of age;
- unable to speak or understand English;
- could not see well enough to read the information on the DFL or CIL (needed contact lenses or glasses to read but did not have them available at the time of interview);
- participant or someone else in the household works for a pharmaceutical company;
- participant was a healthcare professional, works as a part of a healthcare practice or had training as a healthcare professional;
- participant or someone else in the household works for a market research or advertising company; or

- participant had participated in a market research study, product label study, or clinical trial in the past 12 months.

5.2.2.3 Subject Enrollment and Disposition

Subjects participating in testing the DFL and CIL in both Phase 1 and Phase 2 were generally representative of the general population (Table 10 and Table 11). In total, 30-33% of subjects were classified as low literacy.

Table 10 - Demographic Characteristics of Subjects Participating in DFL Testing

Characteristic	Phase One N=475	Phase Two N=325
Gender		
- Male	53.7%	47.4%
- Female	46.3%	52.6%
Education		
- 8th grade or less	0.6%	0.9%
- Some high school	9.1%	13.5%
- High school graduate, GED, or certificate	29.3%	26.2%
- Some college or technical school	34.9%	41.2%
- College graduate	21.3%	14.2%
- Post-graduate degree	4.8%	4.0%
Race		
- White	47.8%	49.2%
- Black or African American	25.1%	28.9%
- Hispanic	19.2%	15.4%
- Asian	2.9%	0.9%
- Native Hawaiian or Other Pacific Islander	0.6%	0%
- American Indian or Alaska Native	0.8%	1.2%
- Other	3.6%	4.3%
Age (years)		
- Under 18	3.6%	6.5%
- 18 to 24	20.4%	39.4%
- 25 to 34	13.5%	17.5%
- 35 to 44	23.4%	12.9%
- 45 to 54	16.0%	9.8%
- 55 to 64	12.4%	8.0%
- 65 to 74	8.0%	4.3%
- 75 to 84	2.5%	1.5%
- ≥85	0.2%	0.0%
Literacy		
- Normal literacy	69.3%	69.2%
- Low literacy	30.7%	30.8%

Table 11 - Demographic Characteristics of Subjects Participating in CIL Testing

Characteristic	Phase One N=323	Phase Two N=411
Gender		
- Male	53.3%	50.6%
- Female	46.7%	49.4%
Education		
- 8th grade or less	0.3%	1.5%
- Some high school	12.4%	12.9%
- High school graduate, GED, or certificate	30.7%	38.4%
- Some college or technical school	39.0%	30.7%
- College graduate	12.1%	14.1%
- Post-graduate degree	5.6%	2.4%
Race		
- White	47.4%	60.3%
- Black or African American	24.5%	16.1%
- Hispanic	16.1%	17.0%
- Asian	2.8%	2.4%
- Native Hawaiian or Other Pacific Islander	0.9%	0.2%
- American Indian or Alaska Native	0.6%	0.5%
- Other	7.7%	3.4%
Age (years)		
- Under 18	7.1%	4.9%
- 18 to 24	28.2%	29.0%
- 25 to 34	18.3%	13.9%
- 35 to 44	13.3%	17.8%
- 45 to 54	13.3%	12.9%
- 55 to 64	9.3%	12.2%
- 65 to 74	8.4%	6.3%
- 75 to 84	1.9%	2.9%
- ≥85	0.3%	0.2%
Literacy		
- Normal literacy	67.8%	68.9%
- Low literacy	32.2%	31.1%

5.2.3 Findings on Testing DFL Comprehension

In Phase 1, the primary communication objective (the need to prepare the pump before first use) was understood by 80.3% (95% CI: 76.5%-83.8%) of the all participants (comprehension was 83.2% among normal literacy and 74.0% among low literacy participants) with the lower CI failing to meeting pre-specified 80% criterion for success. Based upon participant feedback after Phase 1, modifications to the DFL were made for additional testing in Phase 2. In particular, participants failed to understand the meaning of the "pump must be prepared," thinking that "preparation" implied the need to mix components, and interpreted the "shake well" on the display panel to be part of the preparatory method. Modifications were made to the DFL to make the language more specific, with a clearer organizational structure to allow for ease of recognition.

In Phase 2, testing of the modified labeling text for the primary communication objective (the need to prime the pump before first use) was correctly understood by 86.8% (95% CI: 82.6%-90.3%) of the participants, meeting the 80% criterion set for success. Comprehension was 93.3% among normal literacy and 72.0% among low literacy participants. All secondary communication objectives and other messages were understood by participants at the targeted 80% level or above (Table 12).

Table 12 - Findings for Label Comprehension Study of Communication Objectives in DFL

DFL Key Message	Overall Score (95% CI) Sample Size	Normal Literacy (95% CI) Sample Size	Low Literacy (95% CI) Sample Size
DFL Primary Communication Objective			
Get a new bottle of Nasacort ready (primed) before first use [a]	86.8% (82.6%, 90.3%) N=325	93.3% (89.2%, 96.2%) N=225	72.0% (62.1%, 80.5%) N=100
DFL Secondary Communication Objectives			
Ask a doctor before use if you have had recent nasal ulcers, nasal surgery or nasal injury that have not healed	87.1% (82.9%, 90.5%) N=325	89.3% (84.5%, 93.0%) N=225	82.0% (73.1%, 89.0%) N=100
Ask a doctor before use if you are using an asthma medicine or a prescription steroid medicine	88.6% (85.4%, 91.3%) N=475	92.1% (88.6%, 94.8%) N=329	80.8% (73.5%, 86.9%) N=146
Ask a doctor before use if you have or had glaucoma or cataracts	88.2% (85.0%, 91.0%) N=475	91.8% (88.3%, 94.5%) N=329	80.1% (72.7%, 86.3%) N=146
Stop use and ask a doctor if you have an allergic reaction, such as a rash, problems swallowing or breathing, swelling of your lips, face or tongue. Seek medical help right away	97.7% (95.9%, 98.8%) N=475	99.4% (97.8%, 99.9%) N=329	93.8% (88.6%, 97.1%) N=146
Stop use and ask a doctor if you have, or come into contact with someone who has, chickenpox, measles, or tuberculosis	92.0% (89.2%, 94.3%) N=475	95.4% (92.6%, 97.4%) N=329	84.2% (77.3%, 89.7%) N=146

DFL Key Message	Overall Score (95% CI) Sample Size	Normal Literacy (95% CI) Sample Size	Low Literacy (95% CI) Sample Size
DFL Other Communication Objectives			
Temporarily relieves these symptoms of hay fever or other respiratory allergies: nasal congestion, sneezing, runny nose, itchy nose	98.5% (97.0%, 99.4%) N=475	99.4% (97.8%, 99.9%) N=329	96.6% (92.2%, 98.9%) N=146
Dosing (sprays/nostril) for Ages 12 and older	98.7% (97.3%, 99.5%) N=475	99.4% (97.8%, 99.9%) N=329	97.3% (93.1%, 99.2%) N=146
Frequency of dosing (how many times a day) for ages 12 and older	92.2% (89.4%, 94.4%) N=474	93.9% (90.7%, 96.2%) N=328	88.4% (82.0%, 93.1%) N=146
Dosing for ages 6 to under 12	98.7% (97.3%, 99.5%) N=475	99.7% (98.3%, 100%) N=329	96.6% (92.2%, 98.9%) N=146
Dosing for ages 2 to under 6	96.2% (94.1%, 97.7%) N=472	97.0% (94.5%, 98.5%) N=328	94.5% (89.4%, 97.6%) N=145
Frequency of dosing (how many times a day) for ages 2 to under 6	95.3% (93.0%, 97.1%) N=472	96.9% (94.4%, 98.5%) N=327	91.7% (86.0%, 95.7%) N=145
May reduce dose if symptoms improve (may use 1 or 2 sprays/nostril/day)	92.8% (90.1%, 95.0%) N=475	93.6% (90.4%, 96.0%) N=329	91.1% (85.3%, 95.2%) N=146
Do not use if under 2 years of age	91.2% (88.2%, 93.6%) N=475	92.7% (89.3%, 95.3%) N=329	87.7% (81.2%, 92.5%) N=146
Action if symptoms do not improve in 1 week	87.6% (84.3%, 90.4%) N=475	89.1% (85.2%, 92.2%) N=329	84.2% (77.3%, 89.7%) N=146
Ask a health professional before use if breast feeding	88.6% (85.4%, 91.3%) N=475	91.2% (87.6%, 94.0%) N=329	82.9% (75.8%, 88.6%) N=146
Read insert (inside package) on how to: • Get a new bottle ready (primed) before first use • Prime bottle again if not used for more than 2 weeks • Use the spray • Clean the spray nozzle	88.0% (84.0%, 91.3%) N=325	91.6% (87.1%, 94.8%) N=225	80.0% (70.8%, 87.3%) N=100
Time to get some symptom relief	95.1% (92.1%, 97.2%) N=325	96.9% (93.7%, 98.7%) N=225	91.0% (83.6%, 95.8%) N=100
Time to get 24-hour symptom relief	83.0% (78.4%, 86.9%) N=323	87.9% (82.9%, 91.9%) N=223	72.0% (62.1%, 80.5%) N=100

DFL Key Message	Overall Score (95% CI) Sample Size	Normal Literacy (95% CI) Sample Size	Low Literacy (95% CI) Sample Size
Do not use if you are allergic to any of the ingredients	87.7% (84.4%, 90.5%) N=472	90.8% (87.2%, 93.7%) N=327	80.7% (73.3%, 86.8%) N=145

Note: The table presents the final results from Phases 1 or 2. Sample sizes vary by phase of final testing.
[a] Primary end-points were evaluated on the basis of the lower bound of the 95% CI exceeding 80%

As shown in Table 12, all but one of the 20 DFL messages tested demonstrated comprehension at specified levels with the lower bound of the 95% confidence interval exceeding 80%. The one exception was an informational statement that "it may take up to one week of daily use for 24-hour symptom relief," for which comprehension was 83% and the lower bound of the confidence interval was 78.4%.

5.2.4 Findings on Testing CIL Comprehension

In Phase 1, testing the primary communication objective for the CIL failed to reach prespecified criteria for success with 71.5% (95% CI 66.2%, 76.4%) of all participants understanding how to prepare the pump. Participant feedback helped clarify communication errors leading to the modification of the CIL for testing in Phase 2. In general, the same issues with the DFL were noted with the CIL and modifications were made to make the CIL more specific, with better organization. In Phase 2, the primary communication objective met success criteria with 88.6% (95% CI 85.1%, 91.5%) of all participants understanding how to prepare the pump.

Table 13 - Findings for Communication Objectives with CIL

CIL Key Message	Overall Score (95% CI) Sample Size	Normal Literacy (95% CI) Sample Size	Low Literacy (95% CI) Sample Size
CIL Primary Communication Objective			
Before first use, a new bottle must be primed a	88.6% (85.1%, 91.5%) N=411	94.3% (91.0%, 96.7%) N=283	75.8% (67.4%, 82.9%) N=128
CIL Secondary Communication Objectives			
If a bottle is not used for more than 2 weeks, prime bottle again	89.5% (86.2%, 92.3%) N=411	96.5% (93.6%, 98.3%) N=283	74.2% (65.7%, 81.5%) N=128
If the pump does not spray properly, the nozzle may be blocked. Clean the nozzle.	96.0% (93.2%, 97.8%) N=323	98.2% (95.4%, 99.5%) N=219	91.3% (84.2%, 96.0%) N=104
If the pump does not spray properly: Never try to unblock the nozzle with a pin or any object	95.7% (92.8%, 97.6%) N=323	97.3% (94.1%, 99.0%) N=219	92.3% (85.4%, 96.6%) N=104

CIL Key Message	Overall Score (95% CI) Sample Size	Normal Literacy (95% CI) Sample Size	Low Literacy (95% CI) Sample Size
CIL Other Communication Objectives			
If you get the spray in your eyes, rinse well with water	95.0% (92.0%, 97.1%) N=321	95.4% (91.7%, 97.8%) N=218	94.2% (87.8%, 97.8%) N=103
Adults should supervise use in children	91.7% (88.6%, 94.2%) N=411	95.8% (92.7%, 97.8%) N=283	82.8% (75.1%, 88.9%) N=128
If you forget a dose, use only as directed. DO NOT DOUBLE DOSE	87.3% (83.7%. 90.4%) N=410	91.5% (87.6%, 94.5%) N=283	78.0% (69.7%, 84.8%) N=127
Aim nozzle toward back of nose. Do NOT spray toward nasal septum (the wall between the 2 nostrils)	94.6% (92.0%, 96.6%) N=411	97.2% (94.5%, 98.8%) N=283	89.1% (82.3%, 93.9%) N=128

Note: The table presents the final results in Phases 1 or 2. Sample sizes vary by phase of final testing.
[a] Primary end-points were evaluated on the basis of the lower bound of the 95% CI exceeding 80%

As shown in Table 13, all 8 CIL messages tested demonstrated comprehension at specified levels, with the lower bound of the 95% confidence interval exceeding 80%. The study demonstrated that the proposed CIL is well-understood.

5.3 FINDINGS IN LABEL COMPREHENSION STUDY OF GROWTH STATEMENTS

To develop the most appropriate language to inform consumer about the potential to decrease growth velocity in prepubescent children, a qualitative study of consumer understanding of language for a growth statement was conducted. This led to proposed language containing 2 components: 1) encouraging the parent or caregiver to inform the physician about the child's use of the product and 2) an informational statement about the potential for growth effects in children.

The proposed growth language was incorporated into the previously tested DFL and tested in a separate label comprehension study. Participants viewed the entire DFL label, but the testing focused on the statement related to growth.

Like the DFL and CIL, these statements were tested, modified, and re-tested over two phases of testing. The final language was as follows:

• *Warnings* section:

When using this product

• in children 2 to under 12 years of age:

- tell your child's doctor when he/she starts using this medication

- this medication may temporarily slow the rate of growth in some children

• Directions section:

In the directions table, dosing instructions for children 6 to under 12 years of age and children 2 to under 6 years of age, the following was added:

- when starting use, tell your child's doctor

The primary end-point for this label comprehension study for Growth Effects was consumer comprehension of the following:

- tell your child's doctor when he/she starts using this medication

- this medication may temporarily slow the rate of growth in some children

The predefined performance criterion was comprehension results where the lower bound of the 95% confidence interval was 80% or better for both primary communication messages. As was the case for the DFL, the statements were tested in two phases; revisions were made between phases, based on findings and feedback from Phase 1. Final results after Phase 2 were as follows: The instruction to tell your child's doctor when he/she starts using Nasacort AQ was understood by 96.6% (95% CI 93.9%, 98.3%) of participants. The informational statement that this medication may temporarily slow the rate of growth in some children was understood by 78.7% (95% CI 73.7%, 83.1%) of participants, with the lower bound of the 95% confidence interval falling below 80% to 73.7%.

To further understand the reason why the informational statement was less understood as compared to the directional statement, a review of the verbatim responses from these participants who gave answers deemed incorrect was conducted. This review suggested that participants did not actually misunderstand the growth statement but rather seemed to have difficulty finding it on the label. It appeared that participants more easily found the "tell your child's doctor" instruction, which were repeated in the Directions section, but had a harder time finding the reason for telling the doctor in the Warnings. Of these two communication messages, the more important message is to tell the child's doctor at the start of using the medication, and that message was understood by nearly all participants. While fewer participants correctly responded to the reason why one should talk to the doctor, the physician can provide counsel regarding the potential for growth effects if consumers follow the direction to inform the child's doctor.

5.4 HUMAN FACTORS STUDY

5.4.1 Summary of Findings

- Three cohorts of consumers were included in the test: Adults (who would administer the medication to themselves), Caregivers (who would be administering the medication to young children), and Youth (who might be administering it under adult supervision).

Results are reported combining results for all, three participant cohorts. Testing of pump operation found that 82%, 85%, and 76% of participants successfully primed, re-primed and cleaned the Nasacort AQ Nasal Spray pump respectively.

- Participant failure to maintain the pump correctly mostly resulted from not reading the CIL instructions or forgetting to do a step, rather than from failure to understand the instructions. Most of those who failed to demonstrate these high-level functions successfully were able to perform them after they were asked to read the instructions thoroughly.

- The impact of failing to perform the tested functions of maintaining the Nasacort AQ Nasal Spray pump correctly is self-limited and minimal, with no safety risk for consumers.

5.4.2 Study Methodology

The study was designed to conform to the FDA draft guidance to industry entitled: Applying Human Factors and Usability Engineering to Optimize Medical Device Design (June 22, 2011).

The study consisting of one-on-one sessions, during which the moderator gave participants, representing potential users, a series of tasks to perform and record their behavior. The sessions lasted up to 60 minutes each.

The study focused on the three high-level functions or tasks requested by the FDA (preparation, maintenance, and cleaning) and evaluated whether consumers (including caregivers, youths, and adults) could correctly demonstrate the steps for these three procedures. In addition, the study also focused on evaluating any patterns of use failures or difficulties that could be eliminated or reduced by modifications to the CIL.

No actual administration of product occurred during the study. Subjects were asked to show how they would maintain the device by engaging in the behavior they would exhibit in relevant scenarios using a bottle filled with saline. Subjects also described what they would do in each scenario under study.

The following standardized scoring was used to record participant behavior on each task:

- **C** = **C**omplete with no issues and met criteria
- **CI** = **C**omplete with **I**ssues (e.g., confusion, frustration)
- **DNC** = **D**id **N**ot **C**omplete but not necessarily a failure (e.g., did not shake product)
- **F = F**ailed (e.g., did not recognize that an incomplete dose had been given)

For each behavior rated CI, DNC, or F, the moderator probed for the root cause of any issues that were observed.

5.4.3 Findings

The study enrolled 16 adults (21 years of age or older), 20 caregivers of children aged 2-12, and 16 youth aged 12 through 20. The latter two age groups were chosen based on the ages identified in the FDA draft guidance to industry entitled: Premarket Assessment of Pediatric

Medical Devices (May 14, 2004). Overall, there was no meaningful difference in the performance of participants between groups (caregivers, youths, and adults). Therefore, the data from all 3 groups were analyzed together. Of the total study population, 62.7% were female and of those participating that were older than 18, about 12% were considered low-literacy by the REALM test.

No participants received scores of CI (completed with issues) or F (failed). The study evaluated performance of three high-level functions, or tasks. Each task consisted of separate steps that were evaluated individually. A summary of the findings follows in which the percentage of participants who correctly executed each step is presented. The predefined critical steps within each task are noted below in bold font.

- High-level function/task: Preparation (Priming the bottle for first use):

  Step 0: Recognize need to prime a bottle before first use: 100%

  Step 1: Remove cap: 100%

  Step 2: Shake bottle: 91%

  Step 3: **Press and release spray nozzle until a fine mist is produced**: 82% of participants performed this step correctly. Of those that did not perform the step correctly, 4 participants sprayed (some liquid came out) but did not achieve a fine mist. Inclusion of these participants increased the correct performance to 90%.

- High-level function/task: Maintenance (Re-prime the bottle if not used for more than 2 weeks):

  Step 0: Recognize need to re-prime after 2 weeks of non-use: 87%

  Step 1: Remove cap: 96%

  Step 2: Shake bottle: 79%

  Step 3: **Press and release spray nozzle until a fine mist is produced**: 85%

- High-level function/task: Cleaning (Clean spray nozzle):

  Step 0: Recognize need to clean nozzle to fix a clog: 94%

  Step 1: Remove spray nozzle from bottle: 92%

  Step 2: **Rinse spray nozzle only under warm water:** 80%

  Step 3: Shake or tap to remove excess water: 90%

  Step 4: Re-attached spray nozzle to bottle: 91%

  Step 5: **Press and release spray nozzle until a fine mist is produced**: 83%

  Steps 2 and 5: Completed both critical steps for cleaning: 76%

Debriefing indicated that when participants did not perform a step, this typically resulted from not reading the CIL instructions or forgetting to do a step, rather than from failure to understand the instructions. Most of those who failed to demonstrate these high-level functions successfully were able to perform them after they were asked to read the instructions thoroughly, suggesting that the instructions were adequate to direct consumer behavior in these tasks.

The observed performance in the human factors study was evaluated in light of the expected consequences of consumers not completing the functions tested. Priming the pump is intended to assure that a consumer gets the full dose on initial application with a new bottle or one that has not been used for 2 weeks. If the pump is not completely primed, the initial sprays might not deliver the full dose, but this would be corrected after a few sprays. Similarly, rinsing the nozzle is meant to clear any obstruction so that a full dose can be delivered. If a clogged nozzle is not fully cleaned, the dose delivered might be less than intended. In all cases, not following the directions for these pump maintenance task would not pose any safety risk to the user.

6 BENEFIT RISK ASSESSMENT OF OTC NASACORT AQ

6.1 ALLERGIC RHINITIS: PREVALENCE AND BURDEN OF THE CONDITION

Allergic rhinitis (AR) is an IgE mediated inflammatory response to aeroallergens (e.g., pollen, animal dander) that affects all age groups. This inflammatory condition is highly prevalent, affecting up to 60 million Americans (8) (9). AR is characterized by nasal and ocular symptoms (sneezing, runny nose, itchy nose, nasal congestion, itchy and watery eyes) among which, sufferers identify nasal congestion as the most bothersome symptom. AR is associated with sleep disturbance, impaired performance and productivity, and a substantial negative impact on quality of life, affecting emotional well-being and social behavior (10) (1). Nasal congestion is thought to be the leading symptom responsible for rhinitis-related sleep problems (35). Approximately one third (~30%) of patients with AR report that AR symptoms have caused them to miss work and half (~51%) reported that AR adversely affects their daily lives to some or to a moderate extent (2). In children, AR interferes with quality of sleep, outdoor activities, and even performance at school (1).

6.2 AR DIAGNOSIS AND TREATMENT LANDSCAPE

The clinical symptoms of nasal congestion, runny nose, sneezing and itchy nose in the setting of allergen exposure is often sufficient to identify AR. Consumers can self-diagnose nasal allergies from these clinical symptoms and therefore AR (i.e., 'hay fever and other upper respiratory allergies') is considered by the FDA as a condition that is self-recognizable and self-treatable.

An array of AR therapies is available in the prescription setting: immunotherapy for AR prevention and pharmacotherapies including intranasal corticosteroids (INS), oral leukotriene inhibitors, intranasal antihistamines, intranasal anticholinergics. Many OTC products, both oral dosage forms (e.g. tablet) and nasal sprays, are approved by the FDA for the consumer to self-treat their AR symptoms. Among these are first and second generation antihistamines, chromones and nasal decongestants. Among all pharmacotherapies, both OTC and prescription, INS are considered the most effective medication class for treatment of AR by the allergy professional societies (5); INS effectively treat all 4 nasal allergy symptoms, including nasal congestion.

6.3 MEDICAL NEED FOR OTC AVAILABILITY OF NASACORT AQ

Even among consumers who have received a diagnosis of AR from a HCP, a majority use OTC medications for treatment of AR. Yet, many of these same individuals are not very satisfied with the efficacy of their OTC medications (13). Oral antihistamines (OAH) are the most common OTC medication class used by consumers for AR. OAH are indicated for treatment of ocular symptoms of AR but are not indicated for the treatment of nasal congestion. Some antihistamine products may cause drowsiness, which can impair ability to drive and work, and may cause excitability, especially in children. INS are not sedating. INS, including Nasacort AQ, have consistently demonstrated superior efficacy compared to OAH for improvement of nasal AR symptoms, including nasal congestion (3) (4) (5).

Oral decongestants (such as pseudoephedrine and phenylephrine) can reduce nasal congestion. But pseudoephedrine, which data suggests is more effective than phenylephrine (11), has restricted consumer availability because of its potential for diversion to the manufacture of methamphetamine. In some states, pseudoephedrine is only available by prescription. Additionally, oral decongestant products include warnings to ask a doctor before use if a consumer has any of the following conditions: heart disease, thyroid disease, glaucoma, high blood pressure, diabetes, trouble urinating due to an enlarged prostate. Intranasal decongestants, such as oxymetazoline, are effective, but should not be used beyond 3 days because of the potential for rebound symptoms, 'rhinitis medicamentosa.' Oral antihistamines are also available OTC combined with oral decongestants. But, as noted for single agent oral decongestants, all such products containing pseudoephedrine currently have restricted consumer availability.

For the pediatric population OTC products are available, but have certain limitations. Intranasal cromolyn needs to be taken every 4 – 6 hours. Once-a-day antihistamines are available for children down to age 2, but are not indicated for nasal congestion. Oral antihistamines can cause sedation or paradoxically even excitability in children. Some OTC decongestants, including phenylephrine nose drops, can be used down to age 2, but must be applied several times a day. Oral OTC products that combine antihistamines and decongestants have age restrictions. Combination products containing first generation antihistamines are indicated down to age 6, without consulting a doctor. Combination products containing second generation antihistamines are either not indicated for children under age 12, or first require consultation with a doctor.

Over-the-counter medications provide ready access to treatment for millions with allergic rhinitis. But, there are gaps in the current OTC treatment environment, for both adults and children. As reported by consumers, many do not experience sufficient relief with current OTC products while they report that for them, efficacy is the most important product characteristic (12). Some products require use multiple times a day, others are limited in duration of use, and some have age limitations. Regulations limit access to many products indicated for the treatment of nasal congestion and for many consumers with common medical conditions these products may not be appropriate or may require physician oversight. Side effects, such as drowsiness, from products in the most commonly used OTC medication class, can interfere with activities of daily living, such as with driving.

OTC status for Nasacort AQ will address a number of these AR treatment gaps. Nasacort AQ can be used down to the age of two and provides symptom relief without sedation with a once daily dose. Nasacort AQ is a monotherapy which addresses the full range of nasal symptoms, including nasal congestion. With OTC availability, consumers would have ready access to this highly effective medication without the need for a prescription or an office visit and the attendant scheduling issues and costs for that visit, including time off from school or work.

6.4 NASACORT AQ NASAL SPRAY: OVERVIEW, EFFICACY AND SAFETY

Triamcinolone acetonide, TAA, the active ingredient in Nasacort AQ, is a well characterized corticosteroid that has been included in numerous prescription products. Corticosteroids are distinct from antihistamines. Corticosteroids have actions on many inflammatory cells and mediators and inflammation is important in the physiologic etiology of allergic rhinitis. As an intranasal product, Nasacort AQ, targets TAA to the nasal mucosa, where nasal allergies start. Targeting therapy to the nasal mucosa minimizes systemic corticosteroid exposure and with it

the potential for undesirable side effects. After intranasal administration, TAA is detectable in the plasma, however, with its short terminal half-life of ~3 hours it becomes undetectable within the 24-hour dosing interval; there is no accumulation with repeat daily dosing. A study of intranasal and oral TAA administration demonstrated that the action of Nasacort AQ in relieving AR symptoms is due to its local action on the nasal mucosa rather than to circulating TAA.

The efficacy of Nasacort AQ, administered once daily for the treatment of AR, is confirmed by 13 studies in adults, adolescents and children as young as 2 years of age that supported the prescription approvals in those populations. Results demonstrated that nasal symptoms improved within the first day of use but that one week of daily use may be needed to obtain maximum benefit. Efficacy assessments for up to one year of use in adults and adolescents and to 6 months of use in children, supported ongoing efficacy with Nasacort AQ in those with perennial nasal allergies. Adults and adolescents self-titrated the Nasacort AQ dose according to label directions (1 or 2 sprays/nostril, 110 or 220 mcg/day) as needed in the study that extended to one-year. In clinical practice, Nasacort AQ is titrated to the minimum dose needed for control of symptoms.

Improvements in quality of life with Nasacort AQ have been demonstrated in studies of adults with seasonal AR. In two double-blind, double-dummy studies Nasacort AQ provided significantly greater relief of nasal AR symptoms and greater improvements in quality of life by a validated scale compared to a second generation oral antihistamine. In an open-label study, Nasacort AQ improved nocturnal quality of life and sleep as assessed by validated scales.

The substantial efficacy of Nasacort AQ for the treatment of AR is accompanied by a favorable and well characterized safety profile. More than 120 million bottles of Nasacort AQ have been dispensed globally. Nasacort AQ has been available by prescription in the US for more than 16 years and is currently available by prescription in more than 60 countries and for nonprescription use in 11 countries, without a change to the favorable safety profile. The safety of Nasacort AQ is supported by the analyses of 43 studies conducted during, and subsequent to the product's development, as well as by ongoing pharmacovigilance.

As a therapy targeted to the nasal mucosa, the most common adverse events of Nasacort AQ are local, particularly in the nose and throat, including epistaxis and nasal discomfort. These events, along with events such as headache, may also be associated with the underlying disease. Epistaxis, i.e., nosebleeds, in particular, is a very common event in the general population even without AR; it can range from a few flecks of blood to a frank nosebleed. Epistaxis is obvious to the individual and almost always self-limited with Nasacort AQ. If severe, however, it may require medical treatment. Nasal septum perforations, which can present as a whistling sound from the nose, have been reported uncommonly with Nasacort AQ.

Immunosuppression, opportunistic infections, or worsening of infections such as measles, tuberculosis, and chickenpox have not been reported with Nasacort AQ. Infections in the nose and adjacent tissue, including sinuses, though reported infrequently, may present with worsening of nasal symptoms such as purulent secretions or pain or fever that direct the patient to medical care. Specific studies have demonstrated that Nasacort AQ has a low potential to suppress the HPA axis in all age groups.

In a study evaluating the effects of growth velocity, which was conducted in accordance with the FDA's Guidance to Industry (27), a small effect on growth velocity (less than ¼ inch) was detected in pre-pubertal children with perennial AR who were treated with Nasacort AQ 110

mcg daily for one year. The study did not follow children to attainment of adult height. Therefore, the potential effect on final adult height is not known. Effects on growth velocity have been observed with other INS.

From clinical studies and post-marketing experience, no signal for bone or glucose metabolism effects was observed. Cases of increased intraocular pressure/glaucoma and cataracts, side effects known to occur with oral corticosteroid use and with age, have been reported over the 16 years of market use. Hypersensitivity reactions have been reported with use of the product and those with a history of allergic reactions to triamcinolone acetonide or any of the nasal spray ingredients should not use Nasacort AQ.

6.5 NASACORT AQ IN THE OTC ENVIRONMENT

An OTC label has been developed to restate information from the prescription label (USPI) in language that is well understood by the consumer. Label comprehension studies support that consumers, even those with low health literacy, can understand the instructions in the proposed Drug Facts Label (DFL) and Consumer Information Leaflet (CIL). The DFL includes specific sections for Purpose, Uses, Directions and Warnings. The CIL will be inside the Nasacort AQ OTC package and provides directions and illustrations for use and maintenance of the nasal spray. Language on the proposed DFL is similar to that of other approved OTC nasal allergy products except where adaptations based on the specific efficacy/safety features of Nasacort AQ were needed. Label instructions, discussed by category below, help mitigate potential risks with use of Nasacort AQ in the consumer environment.

Purpose and Uses

The Purpose for which Nasacort AQ is used, “nasal allergy reliever”, was well understood by consumers. The description of Uses for the product, “temporarily relieves these symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose” is based on language for existing OTC nasal allergy products. Of note, this section differs from that of oral antihistamines because it includes the indication (Uses) for nasal congestion and it omits reference to relief of eye symptoms. The statement of Uses provides clear information for the consumer to identify what this OTC product can do for their nasal allergy symptoms.

In the event a consumer chooses Nasacort AQ for conditions other than nasal allergies, the conditions would not worsen and the consumer would not be placed at additional risk. Common cold symptoms can overlap with nasal allergy symptoms. Colds are limited in time to 7-10 days. INS have been shown not to worsen colds (36). Patients with acute rhinosinusitis and chronic rhinosinusitis, with or without polyps, have nasal symptoms but present differently from patients with nasal allergies. Those with acute rhinosinusitis feel sick, may have fever and purulent nasal secretions. Individuals with chronic rhinosinusitis with or without polyps have persistent nasal and sinus symptoms that may need ongoing care or surgery. In both situations, INS have been shown to not worsen the condition (37) (38). Additionally, the proposed DFL instructs the consumer to stop use of the product and ask a doctor if symptoms do not improve after one week and if they develop symptoms of an infection, such as a persistent fever.

Directions

The directions for dosing of OTC Nasacort AQ are simple, one or two sprays per nostril once daily, and were well understood by consumers. In the prescription environment there were few reports of misuse, abuse, or of taking excessive amounts. The active ingredient in Nasacort AQ is a corticosteroid, not an anabolic steroid. It has no muscle building properties, no immediate psychoactive effects, and results in no rebound effects or sedation. In the event that the entire contents of the bottle (~9 mg of TAA) were administered all at once, via either oral or nasal application, clinically significant systemic adverse events would most likely not result. As an OTC product, Nasacort AQ would have a low potential for abuse.

Warnings

OTC Nasacort AQ is contraindicated for use in individuals with allergy to triamcinolone acetonide or any of the product ingredients. This type of allergy warning, which appears on most OTC products, was well understood in the label comprehension studies. If a consumer were to experience symptoms of a hypersensitivity reaction, they are directed to stop use of the product and seek immediate medical help.

Consumers who are using asthma medications or prescription steroid medications are instructed to ask their doctor before using Nasacort AQ. Many asthma patients also have nasal allergies. While not all asthma patients will be using corticosteroids (oral or inhaled), many will be. The language on the proposed DFL is intentionally broad, to direct consumers to first consult with their doctor if they are taking any asthma medicine or prescription steroid medicine. Similar language can be found on existing OTC products for AR. Consumers taking asthma medicine or prescription steroid medicines will already be under the care of an HCP for access to these medications. These instructions further support the good clinical practice of informing HCPs of all prescription, nonprescription and supplement products that a patient is taking, to assure coordination of their medications and care.

Included in the proposed DFL is an instruction for consumers to consult their doctor before use of Nasacort AQ if they have, or had glaucoma or cataracts. Warnings for consumers with glaucoma to consult a doctor before use are included in a number of OTC products for nasal allergies. Additionally, the proposed DFL instructs consumers to stop use of the product and ask a doctor if they have any change in vision, further enhancing the warning regarding potential ocular effects.

Clinical studies and pharmacovigilance of the prescription product demonstrate that there is a low potential for immunosuppression or HPA axis suppressive effects with Nasacort AQ. Nevertheless, consumers are warned to stop use of the product if they are exposed to certain infections (measles, tuberculosis, chickenpox) or if they develop symptoms of an infection or persistent fever for which they are then directed to a doctor's evaluation. Systemic exposure to TAA and the potential for suppressive effects is minimized by the relatively small intranasal dose and the short half-life of the molecule in plasma with daily dosing. The proposed DFL instructs consumer to use the minimum dose of Nasacort AQ needed to control their symptoms.

The growth velocity study detected a mean growth reduction of less than ¼ inch over the year of daily Nasacort AQ use in children aged 3-9. Effects beyond a year or with different patterns of Nasacort AQ use were not evaluated in the study. The effect detected in the study by comparison of two groups (Nasacort AQ and placebo) may not be discernible in an individual child in the

clinical practice setting. Nevertheless, a statement has been included in the proposed DFL for the parent to inform the child's doctor about use of Nasacort AQ. A statement regarding the potential for growth to slow during Nasacort AQ treatment accompanies that instruction on the proposed label. It is anticipated that regular well-child visits will continue when Nasacort AQ is used in the OTC environment.

Epistaxis occurs frequently in the general population and is one of the more common events experienced by nasal allergy sufferers taking Nasacort AQ. Nosebleeds that are severe or are frequent may require medical attention. Consumers who experience such events are directed to stop use of Nasacort AQ and consult a doctor. The prescription product label instructs patients to aim the nasal spray toward the back of the nose. In development of the proposed OTC label, the instructions have been enhanced to include not spraying the nasal septum, the wall that separates the two nostrils. While the contribution of spraying the nasal septum to the incidence of epistaxis or nasal septum perforation is not definitively known, it is considered prudent to avoid directly spraying the septum when using Nasacort AQ. The proposed language and illustrations have been tested and confirm consumer comprehension of spraying instructions for Nasacort AQ.

6.6 CONCLUSION

Nasacort AQ Nasal Spray effectively treats all four nasal symptoms of allergic rhinitis, including nasal congestion, the symptom that sufferers find most bothersome. The efficacy and safety of the product has been characterized in multiple clinical studies in adults and children, as well as with market experience for over 16 years. The proposed OTC labeling has been developed to ensure consumer understanding of the proper use of the product and to help mitigate potential safety risks. Studies have confirmed consumer understanding of the proposed label.

Sanofi acknowledges that there are different considerations when evaluating the benefits and risks for adults versus the pediatric populations. For adults, the post-marketing safety data for Nasacort AQ is favorable. In the OTC environment, there is a clear need for a more effective AR remedy that treats all four nasal symptoms and Nasacort AQ would address this need. The OTC availability would introduce few risks and these would be mitigated by the OTC labeling. Therefore, the benefits far outweigh the risks for adults.

For children, there is also a clear need for a more effective AR remedy and Nasacort AQ would address this need. The post-marketing safety data for Nasacort AQ is favorable. Although the potential effect on growth requires additional consideration, it does not appear that it is an issue that the OTC availability will impact in an unfavorable way. This is because, despite the fact that the growth study demonstrated an effect in the Nasacort AQ treatment group, this effect is quite small and unlikely to be detectable in an individual child. Therefore, it would almost never be the reason for a change in the treatment management by a child's physician, even in a prescription setting.

In conclusion, the potential safety risks of Nasacort AQ without physician's oversight would not be different or greater than those that currently exist with Nasacort AQ as a prescription product, where Nasacort AQ has demonstrated a favorable benefit-risk profile. These risks are manageable through the OTC labeling. Therefore, the benefits of broader access to a more effective OTC treatment for AR, outweighs the risks in both adults and children.

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8 APPENDICES

1) Appendix 1 Proposed Drug Facts Label
2) Appendix 2 Proposed Consumer Information Leaflet
3) Appendix 3 Nasacort AQ Prescribing Information (USPI)
4) Appendix 4 Listing of Nasacort AQ Clinical Studies
5) Appendix 5 Additional Safety Results from Clinical Studies
6) Appendix 6 Serious Adverse Events from Clinical Studies

APPENDIX 1: PROPOSED DRUG FACTS LABEL

Drug Facts

Active ingredient (in each spray) — **Purpose**

Triamcinolone acetonide 55 mcg ..... Nasal allergy reliever

Uses

temporarily relieves these symptoms of hay fever or other upper respiratory allergies

- nasal congestion
- runny nose
- sneezing
- itchy nose

Warnings

Do not use

- if you are allergic to any of the ingredients

Ask a doctor before use if you

- have had recent nasal ulcers, nasal surgery or nasal injury that have not healed
- are using an asthma medicine or prescription steroid medicine
- currently have an eye infection
- have or had glaucoma or cataracts

When using this product

- **in children 2 to under 12 years of age:**
  - tell your child's doctor when he/she starts using this medication
  - this medication may temporarily slow the rate of growth in some children
- symptom improvement can start within the first day of treatment
- it may take up to one week of daily use for 24-hour symptom relief
- do not share this bottle with anyone else as this may spread germs

Stop use and ask a doctor if

- you have an allergic reaction, such as a rash, problems swallowing or breathing, or swelling of your lips, face or tongue. Seek medical help right away.
- you have, or come into contact with someone who has, chickenpox, measles or tuberculosis
- you have or develop symptoms of an infection such as a persistent fever
- you have any change in vision
- you have severe or frequent nosebleeds

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. ▶

Drug Facts (continued)

Directions

Read insert (inside package) on how to:

- **get a new bottle ready (primed) before first use**
- **prime bottle again if not used for more than 2 weeks**
- **use the spray**
- **clean the spray nozzle**

adults and children 12 years of age and older	■ once daily, spray 2 times into each nostril ■ once your allergy symptoms improve, reduce to 1 spray in each nostril per day
children 6 to under 12 years of age	■ when starting use, tell your child's doctor ■ once daily, spray 1 time into each nostril ■ if allergy symptoms do not improve, increase to 2 sprays in each nostril per day ■ once allergy symptoms improve, reduce to 1 spray in each nostril per day ■ an adult should supervise use
children 2 to under 6 years of age	■ when starting use, tell your child's doctor ■ once daily, spray 1 time into each nostril ■ an adult should supervise use
children under 2 years of age	■ do not use

- do not use more than directed
- shake well before each use
- do not spray into eyes or mouth
- if allergy symptoms do not improve after one week, stop using and talk to a doctor

Other information

- **do not use if sealed package is torn or opened**
- keep package and insert. They contain important information.
- store between 20° to 25° C (68° to 77°F)

Inactive ingredients

benzalkonium chloride, carboxymethylcellulose sodium, dextrose, edetate disodium, hydrochloric acid or sodium hydroxide (for pH adjustment), microcrystalline cellulose, polysorbate 80, water

Questions or comments?

call toll-free **1-800-xxx-xxxx** or www.Tradename.com

APPENDIX 2: PROPOSED CONSUMER INFORMATION LEAFLET

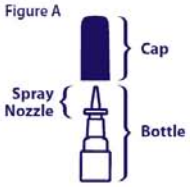
1. IMPORTANT INFORMATION

a. **Read both sides of this insert** for complete instructions on how to get a bottle ready (primed), how to use the spray bottle and how to clean the spray nozzle.

b. Keep this insert as it contains important information.

2. STEPS TO GET A NEW BOTTLE READY FOR USE (PRIMED)

Figure A



A. Before first use, a new bottle must be primed.

a. Remove cap *(Figure A)*.

b. Shake bottle.

c. Press and release spray nozzle until a fine mist is produced, taking care not to spray in face *(as shown in Figure B)*.

B. If Nasacort is not used for more than 2 weeks, prime bottle again.

- **repeat steps "a" through "c" above.**

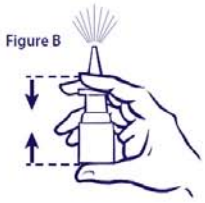
3. USE INSTRUCTIONS

a. Blow nose gently to clear nostrils.

b. Remove cap, then shake bottle.

c. Hold bottle with thumb under bottle and spray nozzle between fingers *(as shown in Figure B)*.

Figure B



d. Close off one nostril with finger.

e. Aim nozzle toward back of nose *(Figure C)*.

DO NOT spray toward nasal septum (the wall between the 2 nostrils) *(Figure D)*.

Figure C

Correct Position

Figure D

Wrong Position

f. While sniffing gently, spray

- twice for adults (and children 12 and older) or
- once for children (ages 2 to under 12).

For complete dosing instructions, See "Table 1 - Directions for use" on next side.

g. Repeat steps "d" through "f" for the other nostril.

h. After using the nasal spray, wipe nozzle with a tissue and replace cap.

NOTE: Avoid blowing nose for 15 minutes after use.

If nozzle does not spray properly, see cleaning instructions on next side.

(continued on next side)

SIDE 1

Table 1 - Directions for use

• ***BEFORE first use, you must get a new bottle ready (primed).*** • ***If bottle is not used for more than 2 weeks, prime bottle again.***	
Dosing	
adults and children 12 years of age and older	• once daily, spray 2 times into each nostril • once allergy symptoms improve, you may reduce to 1 spray in each nostril per day
children 6 to under 12 years of age	• when starting use, tell your child's doctor • once daily, spray 1 time in each nostril • if allergy symptoms do not improve, increase to 2 sprays in each nostril, per day • once allergy symptoms improve, reduce to 1 spray in each nostril per day • an adult should supervise use
children 2 to under 6 years of age	• when starting use, tell your child's doctor • once daily, spray 1 time into each nostril • an adult should supervise use
children under 2 years of age	• do not use
Other important information for use	
• *Do not use more than directed.* • *If you forget a dose, use only as directed. DO NOT DOUBLE DOSE.* • *Do not spray into eyes or mouth.* • *If you get the spray in your eyes, rinse well with water.* • *If allergy symptoms do not improve after one week, stop using and talk to a doctor.* • *Do not share this bottle with anyone else as this may spread germs.*	

4. IF PUMP DOES NOT SPRAY PROPERLY, THE NOZZLE MAY BE BLOCKED

a. Never try to unblock nozzle with a pin or any object *(Figure E)*.

b. Clean the nozzle as shown below.

Figure E

5. CLEANING INSTRUCTIONS

a. Gently pull spray nozzle away from bottle *(Figure F)*.

Figure F

b. Rinse **SPRAY NOZZLE ONLY** under warm water *(Figure G)*.

Figure G

c. Shake or tap to remove excess water.

d. Re-attach spray nozzle to bottle.

e. Press and release spray nozzle until a fine spray is produced, taking care not to spray in face.

Nasacort pump is now ready to use.

Where can I get more information?
1-800-633-1610 or visit www.Nasacort.com

Store between 20° - 25° C (68° - 77° F)

Distributed By: Chattem, Inc.
(part of the sanofi-aventis Group)
Chattanooga, TN 37409-0219
xxxxxx-xx

SIDE 2

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NASACORT AQ safely and effectively. See full prescribing information for NASACORT AQ.

Nasacort® AQ (triamcinolone acetonide)
Nasal Spray
For intranasal use only. Shake Well Before Using.
Initial U.S. Approval: 1957

----------INDICATIONS AND USAGE----------

- NASACORT AQ Nasal Spray is a corticosteroid indicated for treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------

- *Adults and adolescents ≥ 12 years:* Starting and maximum dose is 220 mcg/day (two sprays in each nostril once daily). (2.1)
- *Children 6 to 12 years of age:* Starting dose is 110 mcg/day (one spray in each nostril once daily). Maximum dose is 220 mcg/day (two sprays per nostril once daily). (2.2)
- *Children 2 to 5 years of age:* Starting and maximum dose 110 mcg/day (one spray in each nostril once daily). (2.2)
- *Priming/Use*: Shake well before each use. Before using for the first time, release 5 sprays into the air away from the face. If the product is not used for more than 2 weeks, release 1 spray into the air before using. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Nasal Spray: 55 mcg triamcinolone acetonide in each spray. Supplied in 16.5 g bottle containing 120 actuations. Each 120 actuation bottle contains 9.075 mg triamcinolone acetonide. (3)

----------CONTRAINDICATIONS----------

- Do not administer to patients with history of hypersensitivity to triamcinolone acetonide or any ingredients of this product. (4)

----------WARNINGS AND PRECAUTIONS----------

- Epistaxis, nasal septal perforation, *Candida albicans* infection, impaired wound healing. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal septal ulcers, nasal surgery, or trauma. (5.1)
- Development of glaucoma or posterior subcapsular cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. (5.2)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patient with the above because of the potential for worsening of these infections. (5.3)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue NASACORT AQ Nasal Spray slowly. (5.4)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving NASACORT AQ Nasal Spray. (5.5, 8.4)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (>2% incidence) were pharyngitis, epistaxis, flu syndrome, cough increased, bronchitis, dyspepsia, tooth disorder, headache, pharyngolaryngeal pain, nasopharyngitis, abdominal upper pain, diarrhea, and excoriation. (6.1)
- Other adverse reactions, including serious adverse reactions, have been reported. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

NASACORT AQ should be used during pregnancy only if potential benefit justifies potential risk to fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: October 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

NASACORT AQ Nasal Spray is indicated for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older.

2. DOSAGE AND ADMINISTRATION

Administer NASACORT AQ Nasal Spray by the intranasal route only. Shake NASACORT AQ Nasal Spray well before each use.

2.1 Adults and Adolescents 12 Years of Age and Older

The recommended starting and maximum dose is 220 mcg per day as two sprays in each nostril once daily. Titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose to 110 mcg per day (one spray in each nostril once a day) has been shown to be effective in maintaining control of the allergic rhinitis symptoms.

2.2 Children 2 to 12 Years of Age

Children 6 to 12 years of age: The recommended starting dose is 110 mcg per day given as one spray in each nostril once daily. Children not responding adequately to 110 mcg per day may use 220 mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 110 mcg once daily.

Children 2 to 5 years of age: The recommended and maximum dose is 110 mcg per day given as one spray in each nostril once daily.

NASACORT AQ Nasal Spray is not recommended for children under 2 years of age.

2.3 Administration Information

Priming: Prime NASACORT AQ Nasal Spray before using for the first time by shaking the contents well and releasing 5 sprays into the air away from the face. It will remain adequately primed for two weeks. If the product is not used for more than 2 weeks, then it can be adequately reprimed with one spray. Shake NASACORT AQ Nasal Spray well before each use.

If adequate relief of symptoms has not been obtained after 3 weeks of treatment, NASACORT AQ Nasal Spray should be discontinued. [*See Warnings and Precautions (5), Patient Counseling Information (17), and Adverse Reactions (6)*]

3. DOSAGE FORMS AND STRENGTHS

NASACORT AQ Nasal Spray is a metered-dose pump spray containing the active ingredient triamcinolone acetonide. Each actuation delivers 55 mcg triamcinolone acetonide from the nasal actuator after an initial priming of 5 sprays. Each 16.5 gram bottle (120 actuations) contains 9.075 mg of triamcinolone acetonide. The bottle should be discarded when the labeled-number of actuations have been reached even though the bottle is not completely empty.

4. CONTRAINDICATIONS

NASACORT AQ should not be administered to patients with a history of hypersensitivity to triamcinolone acetonide or to any of the other ingredients of this preparation.

5. WARNINGS AND PRECAUTIONS

5.1 Local Nasal Effects

Epistaxis: In clinical studies of 2 to 12 weeks duration, epistaxis was observed more frequently in patients treated with NASACORT AQ Nasal Spray than those who received placebo [*see Adverse Reactions (6)*].

Nasal Septal Perforation: In clinical trials, nasal septum perforation was reported in one adult patient treated with NASACORT AQ Nasal Spray.

Candida Infection: In clinical studies with NASACORT AQ Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local or systemic therapy and discontinuation of NASACORT AQ Nasal Spray. Therefore, patients using NASACORT AQ Nasal Spray over several months or longer should be examined periodically for evidence of Candida infection or other signs of adverse effects on the nasal mucosa.

Impaired Wound Healing: Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, surgery, or trauma should not use NASACORT AQ Nasal Spray until healing has occurred.

5.2 Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts.

5.3 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or have not been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections, or ocular herpes simplex because of the potential for worsening of these infections.

5.4 Hypothalamic-Pituitary-Adrenal Axis Effects

Hypercorticism and Adrenal Suppression: When intranasal steroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercoticism and adrenal suppression may appear. If such changes occur, the dosage of NASACORT AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

5.5 Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving NASACORT AQ Nasal Spray. To minimize the systemic effects of intranasal corticosteroids, including NASACORT AQ Nasal Spray, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [*see Use in Specific Populations (8.4*)].

6. ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Epistaxis, *Candida albicans* infection, nasal septal perforation, impaired wound healing [*see Warnings and Precautions (5.1)*]
- Glaucoma and Cataracts [*see Warnings and Precautions (5.2*)]
- Immunosuppression [*see Warnings and Precautions (5.3)*]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see Warnings and Precautions (5.4, 5.5), Use in Specific Populations (8.4)*]

6.1 Clinical Trials Experience

In placebo-controlled, double-blind, and open-label clinical studies, 1483 adults and children 12 years and older received treatment with NASACORT AQ Nasal Spray. These patients were treated for an average duration of 51 days. In the controlled trials (2-5 weeks duration) from which the following adverse reaction data are derived, 1394 patients were treated with NASACORT AQ Nasal Spray for an average of 19 days. In a long-term, open-label study, 172 patients received treatment for an average duration of 286 days. Adverse reactions from 12 studies in adults and adolescent patients 12 to 17 years of age receiving NASACORT AQ Nasal Spray 27.5 mcg to 440 mcg once daily are summarized in Table 1.

In clinical trials, nasal septum perforation was reported in one adult patient who received NASACORT AQ Nasal Spray.

Table 1 - Adverse drug reactions > 2% and greater than placebo with NASACORT AQ Nasal Spray 220 mcg treatment in studies in adults and adolescents 12 years and older

	Placebo (N=962)	NASACORT AQ 220 mcg (N=857)
Adverse reaction	%	%
Pharyngitis	3.6	5.1
Epistaxis	0.8	2.7
Cough increased	1.5	2.1

Coding dictionary for adverse events is Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).

A total of 602 children 6 to 12 years of age were studied in 3 double-blind, placebo-controlled clinical trials. Of these, 172 received 110 mcg/day and 207 received 220 mcg/day of NASACORT AQ Nasal Spray for two, six, or twelve weeks. The longest average durations of treatment for patients receiving 110 mcg/day and 220 mcg/day were 76 days and 80 days, respectively. One percent of patients treated with NASACORT AQ were discontinued due to adverse experiences. No patient receiving 110 mcg/day and one patient receiving 220mcg/day discontinued due to a serious adverse event. A similar adverse reaction profile was observed in pediatric patients 6-12 years of age as compared to adolescents and adults with the exception of epistaxis which occurred in less than 2% of the children studied. Adverse reactions from 2 studies in children 4 to 12 years of age receiving NASACORT AQ Nasal Spray 110 mcg once daily are summarized in Table 2.

Table 2 - Adverse drug reactions > 2% and greater than placebo with NASACORT AQ Nasal Spray 110 mcg treatment in US studies in patients 4 to 12 years of age

	Placebo (N=202)	NASACORT AQ 110 mcg (N=179)
Adverse reaction	%	%
Flu syndrome	7.4	8.9
Cough increased	6.4	8.4
Pharyngitis	6.4	7.8
Bronchitis	1.0	3.4
Dyspepsia	1.0	3.4
Tooth disorder	1.0	3.4

Coding dictionary for adverse events is Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).

A total of 474 children 2 to 5 years of age were studied in a 4-week double-blind, placebo-controlled clinical trial. Of these, 236 received 110 mcg/day of NASACORT AQ Nasal Spray for a mean duration of 28 days. No patient discontinued due to a serious adverse event. Adverse reactions from the single placebo-controlled study in children 2 to 5 years of age receiving NASACORT AQ Nasal Spray 110 mcg once daily are summarized in Table 3.

Table 3 - Adverse drug reactions > 2% and greater than placebo with NASACORT AQ Nasal Spray 110 mcg treatment in children 2 to 5 years of age

	Placebo (N=238)	NASACORT AQ 110 mcg (N=236)
Adverse reactions	**%**	**%**
Headache	4.2	5.5
Pharyngolaryngeal pain	4.2	5.5
Epistaxis	5.0	5.1
Nasopharyngitis	3.8	5.1
Abdominal upper pain	0.8	4.7
Diarrhea	1.3	3.0
Asthma	2.1	2.5
Rash	1.7	2.5
Excoriation	0.0	2.5
Rhinorrhea	1.7	2.1

Coding dictionary for adverse events is Medical Dictionary for Regulatory Activities terminology (MedDRA) Version 8.1

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but acute systemic adverse experiences are unlikely. [*See Overdosage (10)*]

6.2 Post-Marketing Experience

In addition to the adverse drug reactions reported during clinical studies and listed above, the following adverse events have been identified during post-approval use of NASACORT AQ Nasal Spray. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Events that have been reported during post-marketing experience include: nasal discomfort and congestion, sneezing, alterations of taste and smell, nausea, insomnia, dizziness, fatigue, dyspnea, decreased blood cortisol, cataract, glaucoma, increased ocular pressure, pruritus, rash, and hypersensitivity.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of NASACORT AQ Nasal Spray in pregnant women. Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. NASACORT AQ Nasal Spray, like other corticosteroids, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Since their introduction, experience with oral corticosteroids in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

In reproduction studies in rats and rabbits, triamcinolone acetonide administered by inhalation produced cleft palate and/or internal hydrocephaly and axial skeletal defects at exposures less than and 2 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis. In a monkey reproduction study, triamcinolone acetonide administered by inhalation produced cranial malformations at an exposure approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis.

8.3 Nursing Mothers

It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when NASACORT AQ Nasal Spray is administered to nursing women.

8.4 Pediatric Use

The safety and effectiveness of NASACORT AQ Nasal Spray has been evaluated in 464 children 2 to 5 years of age, 518 children 6 to 12 years of age, and 176 adolescents 12 to 17 years of age [*see Clinical Studies (14)*]. The safety and effectiveness of NASACORT AQ Nasal Spray in children below 2 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of reduction in growth velocity associated with intranasal corticosteroids, including the impact of final adult height are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including NASACORT AQ Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including NASACORT AQ Nasal Spray, each patient's dose should be titrated to the lowest dosage that effectively controls his/her symptoms.

The potential for NASACORT AQ Nasal Spray to cause growth suppression in susceptible patients and when given at higher than recommended dosages cannot be ruled out.

8.5 Geriatric Use

Clinical studies of NASACORT AQ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

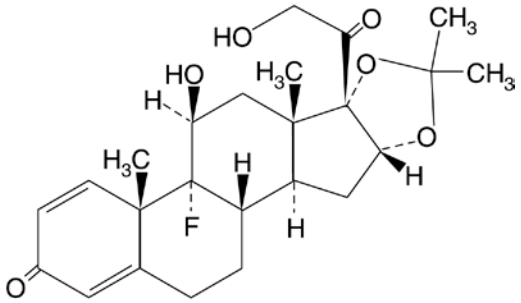
10. OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism [*see Warnings and Precautions (5.4)*]. There are no data on the effects of acute or chronic overdosage with NASACORT AQ Nasal Spray. Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical studies overdose is unlikely to require any therapy other than observation.

Acute overdosing with the intranasal dosage form is unlikely in view of the total amount of active ingredient present and low bioavailability of triamcinolone acetonide. In the event that the entire contents of the bottle were administered all at once, via either oral or nasal application, clinically significant systemic adverse events would most likely not result.

11. DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in NASACORT AQ Nasal Spray, is a corticosteroid with a molecular weight of 434.51 and with the chemical designation 9-Fluoro-11ß,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone ($C_{24}H_{31}FO_6$).



NASACORT AQ Nasal Spray is a thixotropic, water-based metered-dose pump spray formulation unit containing a microcrystalline suspension of triamcinolone acetonide in an aqueous medium. Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, dextrose, benzalkonium chloride, and edetate disodium are contained in this aqueous medium; hydrochloric acid or sodium hydroxide may be added to adjust the pH to a target of 5.0 within a range of 4.5 and 6.0.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Triamcinolone acetonide is a synthetic fluorinated corticosteroid with approximately 8 times the potency of prednisone in animal models of inflammation.

Although the precise mechanism of corticosteroid antiallergic action is unknown, corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

12.2 Pharmacodynamics

In order to determine if systemic absorption plays a role in the effect of NASACORT AQ Nasal Spray on allergic rhinitis symptoms, a two week double-blind, placebo-controlled clinical study was conducted comparing NASACORT AQ, orally ingested triamcinolone acetonide, and placebo in 297 adult patients with seasonal allergic rhinitis. The study demonstrated that the therapeutic efficacy of NASACORT AQ Nasal Spray can be attributed to the topical effects of triamcinolone acetonide.

Adrenal Function: In order to evaluate the effects of systemic absorption on the Hypothalamic-Pituitary-Adrenal (HPA) axis, 3 clinical studies, one each in adults and in children 6-12 years of age and 2-5 years of age, were conducted.

The adult clinical study compared 220 mcg or 440 mcg NASACORT AQ per day, or 10 mg prednisone per day with placebo for 42 days. Adrenal response to a six-hour 250 mcg cosyntropin stimulation test showed that NASACORT AQ administered at doses of 220 mcg and 440 mcg had no statistically significant effect on HPA activity versus placebo. Conversely, oral prednisone at 10 mg/day significantly reduced the response to ACTH.

A study evaluating plasma cortisol response thirty and sixty minutes after 250 mcg cosyntropin stimulation in 80 pediatric patients 6 to 12 years of age who received 220 mcg or 440 mcg (twice the maximum recommended daily dose) daily for six weeks was conducted. No abnormal response to cosyntropin infusion (peak serum cortisol <18 mcg/dL) was observed in any pediatric patient after six weeks of dosing with NASACORT AQ at 440 mcg per day.

In pediatric patients 2 to 5 years of age, HPA axis assessment was performed; however, the results were inconclusive and an effect of NASACORT AQ Nasal Spray on adrenal function in children 2 to 5 years of age cannot be ruled out.

12.3 Pharmacokinetics

Based upon intravenous dosing of triamcinolone acetonide phosphate ester in adults, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.5 L (SD ± 27.5) and clearance was 45.2 L/hour (SD ± 9.1) for triamcinolone acetonide. The plasma half-life of corticosteroids does not correlate well with the biologic half-life.

Pharmacokinetic characterization of the NASACORT AQ Nasal Spray formulation was determined in both normal adult subjects and patients with allergic rhinitis. Single dose intranasal administration of 220 mcg of NASACORT AQ Nasal Spray in normal adult subjects and patients demonstrated minimal absorption of triamcinolone acetonide. The mean peak plasma concentration was approximately 0.5 ng/mL (range: 0.1 to 1.0 ng/mL) and occurred at 1.5 hours post dose. The mean plasma drug concentration was less than 0.06 ng/mL at 12 hours, and below the assay detection limit (the minimum LOQ of the assay was 0.025 ng/ml) at 24 hours. The average terminal half-life was 3.1 hours. The range of mean $AUC_{0-\infty}$ values was 1.4 ng•hr/mL to 4.7 ng•hr/mL between doses of 110 mcg to 440 mcg in both patients and healthy volunteers. Dose proportionality was demonstrated in both normal adult subjects and in allergic

rhinitis patients following single intranasal doses of 110 mcg or 220 mcg NASACORT AQ Nasal Spray. The C_{max} and $AUC_{0-\infty}$ of the 440 mcg dose increased less than proportionally when compared to 110 and 220 mcg doses.

Following multiple dose administration of NASACORT AQ 440 mcg once daily in pediatric patients 6 to 12 years of age, plasma drug concentrations, $AUC_{0-\infty}$, C_{max} and T_{max} were similar to those values observed in adult patients receiving the same dose. Intranasal administration of NASACORT AQ 110 mcg once daily in pediatric patients 2 to 5 years of age exhibited similar systemic exposure to that achieved in adult patients 20 to 49 years of age with intranasal administration of NASACORT AQ at a dose of 220 mcg once daily. Based on the population pharmacokinetic modeling, the apparent clearance and volume of distribution following intranasal administration of NASACORT AQ in pediatric patients 2 to 5 years of age were found to be approximately half of that in adults.

In animal studies using rats and dogs, three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 1.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively). In a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 3.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively).

No evidence of mutagenicity was detected from *in vitro* tests (a reverse mutation test in *Salmonella* bacteria and a forward mutation test in Chinese hamster ovary cells) conducted with triamcinolone acetonide.

In male and female rats, triamcinolone acetonide caused no change in pregnancy rate at oral doses up to 15.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). Triamcinolone acetonide caused increased fetal resorptions and stillbirths and decreases in pup weight and survival at doses of 5.0 mcg/kg and above (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). At 1.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis), it did not induce the above mentioned effects.

13.2 Animal Toxicology and/or Pharmacology

Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. In rats, triamcinolone acetonide was teratogenic at an inhalation dose of 20 mcg/kg and above (approximately 7/10 of the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). In rabbits, triamcinolone acetonide was teratogenic at inhalation doses of 20 mcg/kg and above (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). In monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 500 mcg/kg (approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). Dose-related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects, whereas the effects observed in the monkey were cranial malformations.

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

14. CLINICAL STUDIES

The safety and efficacy of NASACORT AQ Nasal Spray have been evaluated in 10 double-blind, placebo-controlled clinical studies of two- to four-weeks duration in adults and children 12 years and older with seasonal or perennial allergic rhinitis. The number of patients treated with NASACORT AQ Nasal Spray in these studies was 1266; of these patients, 675 were males and 591 were females.

Overall, the results of these clinical studies in adults and children 12 years and older demonstrated that NASACORT AQ Nasal Spray 220 mcg once daily (2 sprays in each nostril), when compared to placebo, provides statistically significant relief of nasal symptoms of seasonal or perennial allergic rhinitis including sneezing, stuffiness, discharge, and itching.

The safety and efficacy of NASACORT AQ Nasal Spray, at doses of 110 mcg or 220 mcg once daily, have also been adequately studied in two double-blind, placebo-controlled studies of two- and twelve-weeks duration in children ages 6 through 12 years with seasonal and perennial allergic rhinitis. These studies included 341 males and 177 females. NASACORT AQ administered at either dose resulted in statistically significant reductions in the severity of nasal symptoms of allergic rhinitis.

The safety and efficacy of NASACORT AQ Nasal Spray in children 2 to 5 years of age with perennial allergic rhinitis with or without seasonal allergic rhinitis was studied in a single 4 week double blind, placebo controlled clinical study with a 24 week open label extension conducted in the United States. The study included 464 patients (266 males and 198 females) 2 to 5 years of age who received at least one dose of study medication (233 placebo, 231 NASACORT AQ 110 mcg once daily). Efficacy was determined over a four-week double-blind, placebo-controlled treatment period and was based on patient's parent or guardian recording of four nasal symptoms (total nasal symptom score, TNSS), congestion, itching, rhinorrhea, and sneezing on a 0-3 categorical severity scale (0=absent, 1=mild, 2=moderate, and 3=severe) once daily. Reflective scoring (rTNSS) required recording symptom severity over the previous 24 hours; the instantaneous scoring (iTNSS) required recording symptom severity at the time just prior to dosing. Baseline symptom severity was comparable between NASACORT AQ and placebo

respectively, for iTNSS (7.52, 7.61) and rTNSS (7.96, 7.87). While the 24-hour iTNSS over the 4-week double-blind period was numerically improved with NASACORT AQ (-2.28) vs. placebo (-1.92), the difference was not statistically significant (difference from placebo -0.36; 95% CI [-0.77, 0.06]; p value = 0.095). For the 24-hour rTNSS over the 4 week double-blind treatment period, NASACORT A Q 110 mcg once daily provided statistically significantly greater improvement from baseline (-2.31) versus placebo (-1.87) (difference from placebo -0.44; 95% CI [-0.84, -0.04]; p value = 0.033).

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NASACORT AQ Nasal Spray, 55 mcg per spray, is supplied in a white high-density polyethylene container with a metered-dose pump unit, white nasal adapter, and patient instructions (NDC 0075-1506-16).

The contents of one 16.5 gram bottle provide 120 actuations. After 120 actuations, the amount of triamcinolone acetonide delivered per actuation may not be consistent and the unit should be discarded**.** Each actuation delivers 55 mcg triamcinolone acetonide from the nasal actuator after an initial priming of 5 sprays [*See Administration Information (2.3)*].
In the Patient Package Information, patients are provided with a check-off form to track usage [*See Patient Counseling Information (17)*].
Keep out of reach of children. Rx only

16.2 Storage

Store at Controlled Room Temperature, 20 to 25°C (68 to 77°F)

17. PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling accompanying the product.

17.1 Local Nasal Effects

Patients should be informed that treatment with NASACORT AQ Nasal Spray may lead to adverse reactions, which include epistaxis and nasal ulceration. Candida infection may also occur with treatment with NASACORT AQ Nasal Spray. In addition, nasal corticosteroids are associated with nasal septal perforation and impaired wound healing. Patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use NASACORT AQ Nasal Spray until healing has occurred [*see Warnings and Precautions (5.1)*].

17.2 Cataracts and Glaucoma

Patients should be informed that glaucoma and cataracts are associated with nasal and inhaled corticosteroid use. Patients should inform his/her heath care provider if a change in vision is noted while using NASACORT AQ Nasal Spray [*see Warnings and Precautions (5.2)*].

17.3 Immunosuppression

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay.

Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections, or ocular herpes simplex [*see Warnings and Precautions (5.3)*].

17.4 Use Daily for Best Effect

Patients should use NASACORT AQ Nasal Spray on a regular once-daily basis for optimal effect. It is also important to shake the bottle well before each use. Do not blow your nose for 15 minutes after using the spray. NASACORT AQ Nasal Spray, like other corticosteroids, does not have an immediate effect on rhinitis symptoms. Although improvement in some patient symptoms may be seen within the first day of treatment, maximum benefit may not be reached for up to one week. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

17.5 Keep Spray Out of Eyes

Patients should be informed to avoid spraying NASACORT AQ Nasal Spray in their eyes.

17.6 Patient Package Information

IMPORTANT: Please read these instructions carefully before using your NASACORT® AQ Nasal Spray

Nasacort® AQ (triamcinolone acetonide)

[na' za-cort]

Nasal Spray

Patient Information:

These instructions provide important information about Nasacort AQ. Ask your healthcare provider or pharmacist if you have any questions.

Important: For use as a nasal spray only.

What is Nasacort AQ?

Nasacort®AQ Nasal Spray is a prescription medicine called a corticosteroid used to treat nasal symptoms of seasonal and year around allergies in adults and children 2 years of age and older. When Nasacort AQ is sprayed in your nose, this medicine helps to lessen the symptoms of sneezing, runny nose, nasal itching and stuffy nose.

Nasacort AQ is not for children under the age of 2 years.

Who should use Nasacort AQ?

Do not use Nasacort AQ if you have had a reaction to triamcinolone acetonide or to any of the other ingredients in Nasacort AQ. See the end of this leaflet for a complete list of ingredients in Nasacort AQ.

What should I tell my healthcare provider before using Nasacort AQ?
Tell your healthcare provider if you are:

- pregnant or planning to become pregnant
- breastfeeding
- exposed to chickenpox or measles
- feeling unwell or have any symptoms that you do not understand

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

How do I use Nasacort AQ?

- Use Nasacort AQ exactly as your healthcare provider tells you.
- You will get the best results if you use Nasacort AQ regularly and without missing a dose. Do not take extra doses.
- Nasacort AQ should be used as a nasal spray only. Do not spray it in your eyes or mouth.
- Your healthcare provider will tell you how and when to use Nasacort AQ. Do not use more Nasacort AQ or take it more often than your healthcare provider tells you.
- The prescription label will usually tell you how many sprays to take and how often. If it does not or if you are unsure, ask your healthcare provider or pharmacist.
    - **For people aged 12 years and older,** the usual dose is **2 sprays in each nostril, one time each day.**
    - **For children aged 6 to 12 years,** the usual dose is **1 spray in each nostril, one time each day.** Your healthcare provider may tell you to take 2 sprays in each nostril **one time each** day.
    - **For children aged 2 to 5 years,** the usual dose is **1 spray in each nostril, one time each day.**
    - **An adult should help a young child use this medicine.**

    Do not stop taking Nasacort AQ without telling your healthcare provider. Before you throw away Nasacort AQ, talk to your healthcare provider to see if you need another prescription. If your healthcare provider tells you to continue using Nasacort AQ, throw away the empty or expired bottle and use a new bottle of Nasacort AQ.

- For detailed instructions, see the "Patient Instructions for Use" at the end of this leaflet.
- Some symptoms may get better on the first day of treatment. It generally takes one week of use to feel the most benefit.

- Protect your eyes from the spray. If you get the spray in your eyes, rinse your eyes well with water.
- If your symptoms do not improve, or if they become worse, contact your healthcare provider.
- Tell your healthcare provider if you have irritation, burning or stinging inside your nose that does not go away when using Nasacort AQ.

What are the possible side effects of Nasacort AQ?

Common side effects of Nasacort AQ include:
Sore throat, headache, and nosebleeds. If you have an increase in nosebleeds after using Nasacort AQ or the inside of your nose hurts, contact your healthcare provider.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

Patient Instructions for Use

Read these instructions carefully before using your Nasacort AQ.

Before using the spray pump bottle:
1. Pull the blue cover and remove the clip from the spray pump unit. See figure A.
If the top part of the spray pump comes off of the bottle
when removing the cover, then re-insert the stem back into the pump.

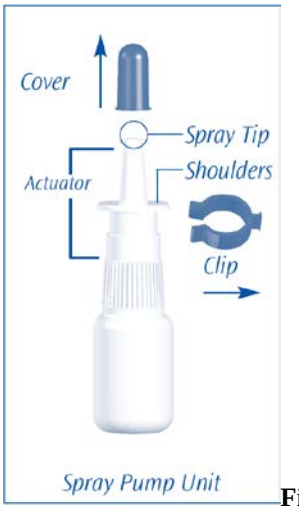


Figure A.

2. Shake the spray pump bottle before each use.

Priming the Spray Pump Bottle

3. Before using the spray pump bottle for the first time, it must be primed. To prime, put your thumb on the bottom of the bottle and your index and middle fingers on the "shoulders" of the bottle, and hold it upright. See figure B.

Figure B

4. Point the bottle away from your eyes. Push the bottle up with your thumb and against your two fingers **firmly** and **quickly** until a fine spray appears. Do this pumping action 5 times.

   Now your spray pump bottle is primed and ready for use.

   A fine mist can only be made by a rapid and firm pumping action.

5. Repeat priming the pump, if it has not been used for more than 2 weeks. To reprime, shake the spray pump bottle and pump it just one time. Now the spray pump bottle is reprimed.

Using the spray:

6. Gently blow your nose to clear it, if needed. For small children, be sure to help them gently blow their nose, as much as possible.

7. Pull off the blue cover and clip as shown in figure C. Shake the spray pump well.

.

Figure C

8. Hold the spray pump firmly, with the index and middle finger on either side of the spray tip. Place your thumb on the bottom of the bottle. **Be careful** so that your fingers will not slip off the spray pump as you spray inside your nose. See figure D.

Figure D

9. Put the spray tip into one side of your nose. The tip should not reach far into the nose. Rest the side of your index finger against your upper lip. Tip your head back a little and aim the spray toward the back of your nose. See figure E.

Figure E

10. Press against the other side of your nose with your finger so the nostril is closed. Pump the spray bottle by pushing on the bottom of the bottle with your thumb **firmly** and **quickly** for the full dose of medicine. Sniff gently at the same time to help the medicine get to the back of your nose. See figure F. Repeat this step for the other side.

Figure F

11. Repeat steps 8, 9 and 10 if your healthcare provider tells you to use more than one spray in each nostril.

12. Do not blow your nose for 15 minutes after using the spray.

13. After use, wipe the nozzle on the spray bottle with a clean tissue, and replace the blue cover.

14. Keep the cover and the clip on the spray pump bottle when not in use.

Cleaning the spray pump bottle:

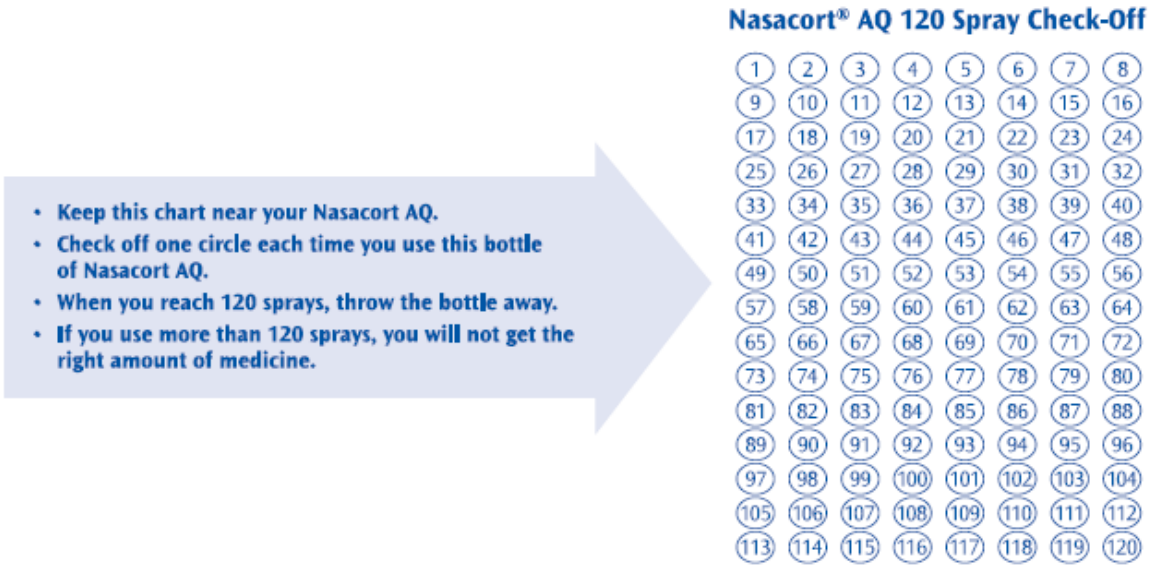
15. To clean the spray pump bottle, remove the blue cover and the spray nozzle only. Soak the cover and spray nozzle in warm water for a few minutes, and then rinse under cold water. See figure G.

Figure G

16. Shake or tap off the excess water and allow to air dry. Once the cap and spray nozzle are dry, put the nozzle back onto the bottle, and prime the bottle as necessary until a fine mist is made. Use the spray as directed by your healthcare provider.

If the spray bottle does not work:
The hole in the tip of the nozzle may be blocked. Never try to unblock the spray hole or enlarge it with a pin or other sharp object. This will make the spray mechanism not work correctly. Changing the size of the opening can change the amount of medicine you or your child will receive. This could cause an overdose of the medicine. To clean nasal spray pump bottle, refer to Step 15.

Important information
Repriming the spray pump is only necessary when it has not been used for more than 2 weeks. To reprime, shake the bottle and only pump the spray bottle one time. Do not reprime if you use the spray more often than every two weeks.
Each Nasacort AQ bottle contains 120 doses of medicine plus a little extra for priming the pump. A check-off chart is included with your Nasacort AQ to help you keep track of the number of sprays. This will help make sure that you receive 120 sprays of Nasacort AQ.



How should I store Nasacort AQ?

- Store Nasacort AQ between 68° to 77°F (20° to 25° C).
- After using 120 sprays, throw the medicine away, as directed by your healthcare provider, even if the bottle is not empty. You may not get enough medicine if you use the bottle after 120 sprays.

Keep Nasacort and all medicines out of the reach of children. General information about the safe and effective use of Nasacort AQ.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information. Do not use Nasacort AQ for a condition for which it was not prescribed. Do not give Nasacort AQ to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about Nasacort AQ. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Nasacort AQ that is written for health professionals.

For more information call 1-800-633-1610.

What are the ingredients in Nasacort AQ?

Active ingredient: triamcinolone acetonide

Inactive ingredients: Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, dextrose, benzalkonium chloride, and edetate disodium are contained in this aqueous medium; hydrochloric acid or sodium hydroxide may be added to adjust the pH to a target of 5.0 within a range of 4.5 and 6.0.

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Bridgewater, NJ 08807
A SANOFI COMPANY

APPENDIX 4: LISTING OF NASACORT AQ CLINICAL STUDIES

Study number (full name)	Study Type	Study design	Subject age (year)	Treatment dose (mcg)	Treatment duration (week)
Pharmacokinetics studies					
004 (RG5029Y-004)	PK in healthy volunteers	Randomized, open-label, 3-way crossover, single center	19 - 35 (healthy)	Triamcinolone acetonide (TAA) : 400 IV infusion, 220 AQN, 220 AQN- charcoal	Single dose
101 (RG5029Y-101)	PK healthy volunteers and AR patients	Randomized, open-label, 4-way crossover, single center, single dose	18 - 50 (healthy), 18 - 44 (AR)	TAA: 110 AQN, 220 AQN, 440 AQN, 440 Intranasal Inhaler	Single dose
122 (RG5029Y-122)	PK in AR patients	Randomized, open-label, 3-way crossover, single center, single dose	19 - 48	TAA: 220 AQN, 660 Oral AQN, 990 Oral AQN	Single dose
1000 (XRG5029C/1000)	PK of single and multiple doses in AR patients	Open-label, multicenter, multidose. Children completed one 5-day treatment period; adults completed two 5-day treatment periods, separated by a 7-day wash-out.	2 - 5, 20 - 49	TAA-AQ: 110 (children), 110 and 220 (adults)	5 days (children), 10 days (adults)
Controlled studies in the original NDA and sNDA					
102 (RG5029Y-102)	HPA axis function in AR patients	Randomized, double-blind, placebo-controlled, parallel group, multicenter	19 - 50	TAA-AQ: 220, 440, placebo, Prednisone 10 mg	6
125 (RG5029Y-125)	HPA-axis function and PK in AR patients	Randomized, double-blind, placebo-controlled, parallel group, multicenter	6 - 12	TAA-AQ: 220, 440, placebo	6
201 (RG5029Y-201)	Dose response in SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	18 - 67	TAA-AQ: 27.5, 55, 110, 220, placebo	2
301 (RG5029Y-301)	Efficacy in ragweed SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	20 - 65	TAA-AQ: 220, placebo	2
302 (RG5029Y-302)	Efficacy in ragweed SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	12 - 17	TAA-AQ: 220, placebo	2

Study number (full name)	Study Type	Study design	Subject age (year)	Treatment dose (mcg)	Treatment duration (week)
303 (RG5029Y-303)	Efficacy in PAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	18 - 82	TAA-AQ: 220, placebo Beclomethasone dipnopionate 400 mcg	3 (22 days)
304 (RG5029Y-304)	Efficacy in mountain cedar SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	19 - 74	TAA-AQ: 55, 220, placebo	2
305(DB) [a] (RG5029Y-305)	Efficacy in PAR	DB period: Randomized, double-blind, placebo-controlled, parallel group, multicenter	11 - 59	TAA-AQ: 220, placebo	4
306 (RG5029Y-306)	Efficacy in SAR with possible dose titration after 2 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter	18 - 82	TAA-AQ: 220/110, placebo, Budesonide 400	4
307 (RG5029Y-307)	Efficacy in SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	16 - 66	TAA-AQ: 220, placebo	3
308 (RG5029Y-308)	Topical vs systemic efficacy in ragweed SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	18 - 67	TAA-AQ: 220, 275 oral, placebo	2
309 (RG5029Y-309)	Efficacy in ragweed SAR with dose titration after 1 week	Randomized, double-blind, placebo-controlled, parallel group, multicenter	18 - 79	TAA-AQ: 220/110, 220/220, placebo	3
312 (RG5029Y-312)	Efficacy in spring grass SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	6 - 12	TAA-AQ: 110, 220, placebo	2
313 (RG5029Y-313)	Efficacy in mountain cedar SAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	18 - 77	TAA-AQ: 220, placebo	2
314 (RG5029Y-314)	Efficacy in PAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	4 - 12	TAA-AQ: 110, 220, placebo	12
315 (RG5029Y-315)	Short-term growth in AR patients	Randomized, double-blind, 4-way crossover, single center	4 - 10	TAA-AQ: 110, 220, placebo Flonase 200	2
3502(DB) [a] (XRG5029C/3502)	Efficacy in PAR	DB period: Randomized, double-blind, placebo-controlled, parallel group, multicenter	2 - 5	TAA-AQ: 110, placebo	4

Study number (full name)	Study Type	Study design	Subject age (year)	Treatment dose (mcg)	Treatment duration (week)
		Other controlled studies			
401-BR1 (NAS.BR1.401)	Safety and efficacy in PAR	Randomized , open-label, active-controlled, parallel-group, multicenter	5-12	TAA-AQ: 110, Beclomethasone	2
402-US1 (XRG5029/US1.402)	Time of onset of sustained relief after the first dose	Randomized, double-blind, placebo-controlled, parallel-group, single center	12 - 63	TAA-AQ: 220, placebo	Single dose
406 (RG5029Y-406)	Efficacy in ragweed SAR	Randomized, single-blind, active-controlled, parallel-group, multicenter	19 - 71	TAA-AQ: 220, Beconase AQ 336	3
435 (NAS.US1.435)	Efficacy, safety, and QoL in SAR	Randomized, single-blind, active-controlled, parallel-group, multicenter	12 - 70	TAA-AQ: 220, Flonase® 200	3
601 (RG5029Y-601)	Efficacy and safety in SAR	Randomized, double-blind, active-controlled, parallel-group, multicenter	12 - 69	TAA-AQ: 220, Claritin 10 mg capsule	4
602 (RG5029Y-602)	Efficacy and safety in SAR	Randomized, double-blind, active-controlled, parallel-group, multicenter	12 - 68	TAA-AQ: 220, Claritin 10 mg capsule	4
703 (RG5029Y-703)	Efficacy in ragweed SAR	Randomized, single-blind, active controlled, parallel-group, multi-center	12 - 69	TAA-AQ: 220, Flonase® 200	3
706 (RG5029Y-706)	Preference and sensory in AR patients	Randomized, double-blind, active controlled, 2-way crossover, multi-center	18 - 82	TAA-AQ: 220, Nasonex® 200	Single dose
4002 (XRG5029C/4002)	Preference and sensory in AR patients	Randomized, double-blind, active-controlled, cross-over, multicenter	18 - 70	TAA-AQ: 220, Flonase® 200, Nasonex® 200	Single dose
4004 (XRG5029C/4004)	Effects on sleep microarousals and quality of sleep in PAR patients	Randomized, double-blind, placebo-controlled, cross-over, single center	22 - 48	TAA-AQ: 220, placebo	4
4006 (XRG5029C/4006)	Preference for Intranasal Corticosteroids in AR patients	Randomized, double-blind, cross-over, active-controlled, single dose	20 - 70	TAA-AQ: 220, Nasonex® 200	Single dose
4007 (XRG5029C/4007)	Efficacy in SAR	Randomized, single-blind, active-controlled, parallel-group, multicenter	12 - 65	TAA-AQ: 220, Rhinocort® 64	1

Study number (full name)	Study Type	Study design	Subject age (year)	Treatment dose (mcg)	Treatment duration (week)
4286 (TRICA_L_04286)	Basal HPA axis Function in AR patients	Randomized, double-blind, placebo-controlled, parallel group, multicenter	2 - 12	TAA-AQ: 110 or 220, placebo	6
40004 (NAS.FR1.40004)	QoL in PAR	Randomized, open-label, active-control, parallel-group, multicenter	18 - 79	TAA-AQ: 220, other PAR treatments in French market	4
49801 (NAS.FR1.49801)	Treatment compliance in PAR	Randomized, open-label, active-controlled, parallel-group, multicenter	14 - 72	TAA-AQ: 220, Beclomethasone 400	6
Long-term studies					
305(DB+OL) [b] (RG5029Y-305)	Efficacy in PAR	DB period: Randomized, double-blind, placebo-controlled, parallel group, multicenter	11 - 59	TAA-AQ: 220, placebo	4
	Long-term safety	OL period: Open-label active treatment follow up for long-term safety	11 - 59	TAA-AQ: 220/110	52
901 (RG5029Y-901)	Effect on nasal mucosa	Randomized, open-label, active-controlled, parallel-group, multicenter	18 - 62	TAA-AQ: 220, Zyrtec® 10 mg, Beconase 400	6 month
3502(DB+OL) [b] (XRG5029C/3502)	Efficacy in PAR	DB period: Randomized, double-blind, placebo-controlled, parallel group, multicenter	2 - 5	TAA-AQ: 110, placebo	4
	Long-term safety	OL period: Open-label, active treatment long-term safety follow up of 3502 (DB)	2 - 5	TAA-AQ: 110	26
3503 (XRG5029C/3503)	Effect on growth of long-term treatment in PAR patients	Randomized, double-blind, placebo-controlled, parallel group, multicenter	3 - 9	TAA-AQ: 110, placebo	52
Other (short-term non-controlled or non-AR) studies					
401-VEN (NAS.401-VEN)	Safety and efficacy in PAR	Open-label, single arm, multicenter	6 - 54	TAA-AQ: 110 - 220	3 month
872 (TRICA_L_00872)	Efficacy and safety in chronic non-allergic and non-infectious rhinitis	Randomized, double-blind, placebo-controlled, parallel-group, multi-centre	18 - 67	TAA-AQ: 220, placebo	12

Study number (full name)	Study Type	Study design	Subject age (year)	Treatment dose (mcg)	Treatment duration (week)
901-US1 (RG5029.US1.901)	Validation of a QoL questionnaire	Open-label, single arm, multicenter	18 - 74	TAA-AQ: 220	2
4005 (XRG5029C/4005)	Effect on quality of sleep in AR patients	Open-label, single arm, multicenter	18 - 65	TAA-AQ: 220	3
4008 (XRG5029C/4008)	Short-term relief of eustachian tube dysfunction and serous otitis media	Randomized, double-blind, placebo-controlled, parallel group, multicenter	6 - 95	TAA-AQ: 220 for ≥12 yrs, 110 for <12 years, placebo	6

AQN=Aqueous Nasal Spray

[a] Both 305(DB) and 3502(DB) had an open-label long-term follow-up period which was listed as long-term study.

[b] Data from first TAA-AQ intake to the end of study for subjects who entered into open-label (OL) period. Subject 0068/0013 in Study 3502 skipped DB period and entered into OL period directly.

APPENDIX 5: ADDITIONAL SAFETY RESULTS FROM CLINICAL STUDIES

Table 1 - Adverse events by PT with PT >=1% in TAA-AQ or placebo group in all placebo controlled studies in adult/adolescent subjects – Safety population

Preferred term n (%)	Placebo (N=955)		TAA-AQ (Total) (N=1388)	
Any class	275	(28.8%)	387	(27.9%)
Headache	70	(7.3%)	80	(5.8%)
Oropharyngeal pain	20	(2.1%)	33	(2.4%)
Epistaxis	8	(0.8%)	28	(2.0%)
Cough	13	(1.4%)	23	(1.7%)
Upper respiratory tract infection	5	(0.5%)	20	(1.4%)
Nasopharyngitis	14	(1.5%)	19	(1.4%)
Sinus headache	10	(1.0%)	16	(1.2%)
Influenza	10	(1.0%)	12	(0.9%)
Sneezing	14	(1.5%)	5	(0.4%)

Table includes subjects from Studies RG5029Y-201, RG5029Y-301, RG5029Y-302, RG5029Y-303, RG5029Y-304, RG5029Y-305 (DB, age>=12 years), RG5029Y-306, RG5029Y-307, RG5029Y-308, RG5029Y-309, RG5029Y-312 (age>=12 years), RG5029Y-313, RG5029Y-314 (age>=12 years).

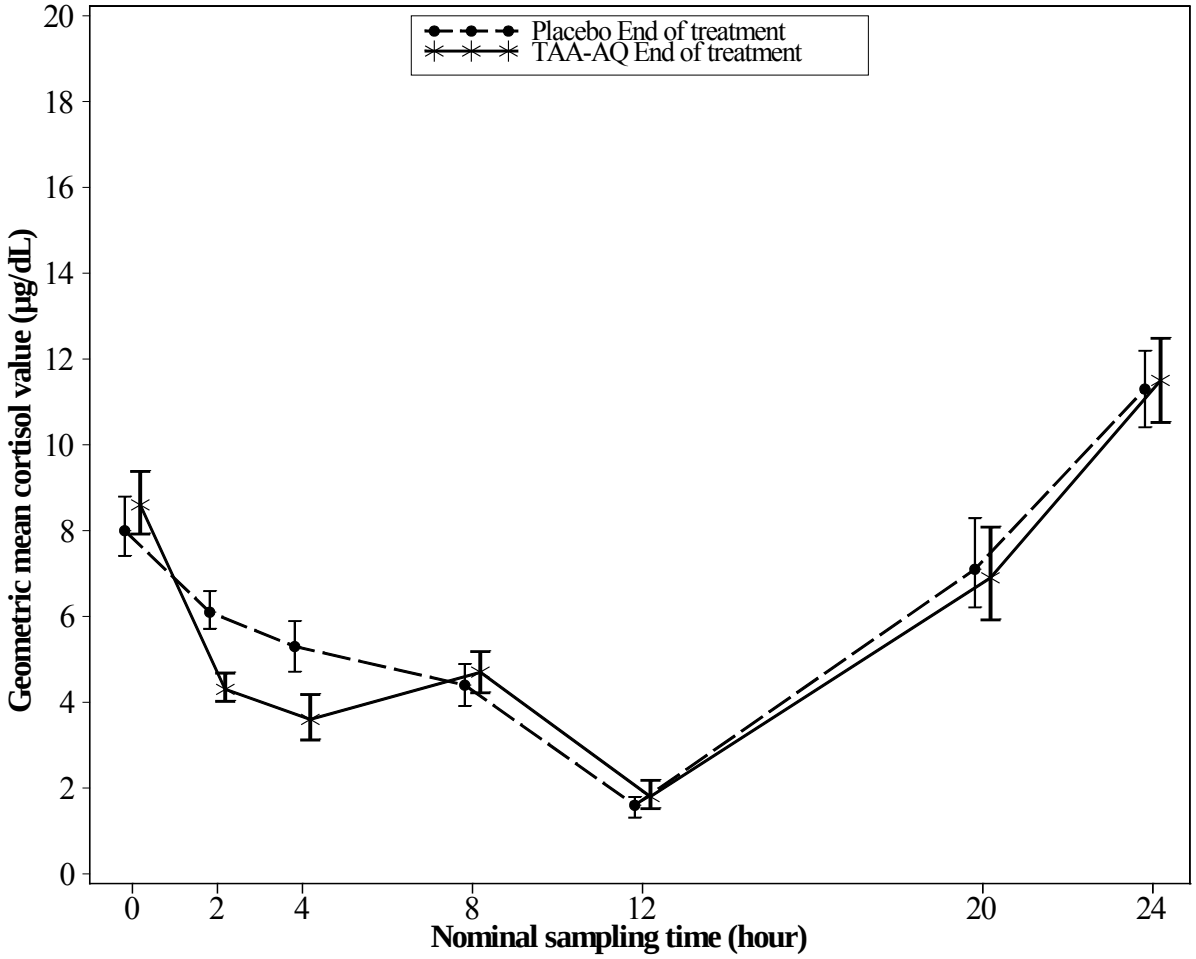
PGM=DEVOPS/XRG5029/OTCNDA/ISS2012_02/REPORT/PGM/aepct1_adcom.sas OUT=REPORT/OUTPUT/ae_pt_teae_plac_adu_1pct_t_x.rtf (20MAR2013 - 16:23)

Table 2 - Adverse events by PT with PT >=1% in TAA-AQ or placebo group in all placebo controlled studies in pediatric subjects – Safety population

Preferred term n (%)	Placebo (N=624)		TAA-AQ (Total) (N=794)	
Any class	328	(52.6%)	419	(52.8%)
Headache	61	(9.8%)	77	(9.7%)
Cough	63	(10.1%)	75	(9.4%)
Pyrexia	68	(10.9%)	70	(8.8%)
Nasopharyngitis	40	(6.4%)	62	(7.8%)
Epistaxis	39	(6.3%)	46	(5.8%)
Upper respiratory tract infection	33	(5.3%)	44	(5.5%)
Oropharyngeal pain	36	(5.8%)	43	(5.4%)
Vomiting	21	(3.4%)	37	(4.7%)
Abdominal pain upper	19	(3.0%)	33	(4.2%)
Influenza	19	(3.0%)	33	(4.2%)
Sinusitis	27	(4.3%)	25	(3.1%)
Asthma	20	(3.2%)	24	(3.0%)
Rash	9	(1.4%)	20	(2.5%)
Viral infection	7	(1.1%)	20	(2.5%)
Pharyngitis streptococcal	14	(2.2%)	18	(2.3%)
Ear infection	18	(2.9%)	17	(2.1%)
Ear pain	17	(2.7%)	16	(2.0%)
Gastroenteritis viral	7	(1.1%)	16	(2.0%)
Rhinorrhoea	14	(2.2%)	14	(1.8%)
Diarrhoea	11	(1.8%)	13	(1.6%)
Bronchitis	6	(1.0%)	12	(1.5%)
Nasal congestion	15	(2.4%)	12	(1.5%)
Viral upper respiratory tract infection	10	(1.6%)	12	(1.5%)
Abdominal discomfort	4	(0.6%)	9	(1.1%)
Conjunctivitis	9	(1.4%)	9	(1.1%)
Otitis media	17	(2.7%)	9	(1.1%)
Arthropod bite	3	(0.5%)	8	(1.0%)
Nasal discomfort	6	(1.0%)	8	(1.0%)
Pain in extremity	8	(1.3%)	7	(0.9%)
Wheezing	9	(1.4%)	7	(0.9%)
Eczema	7	(1.1%)	6	(0.8%)
Urticaria	8	(1.3%)	6	(0.8%)
Lymphadenopathy	9	(1.4%)	3	(0.4%)

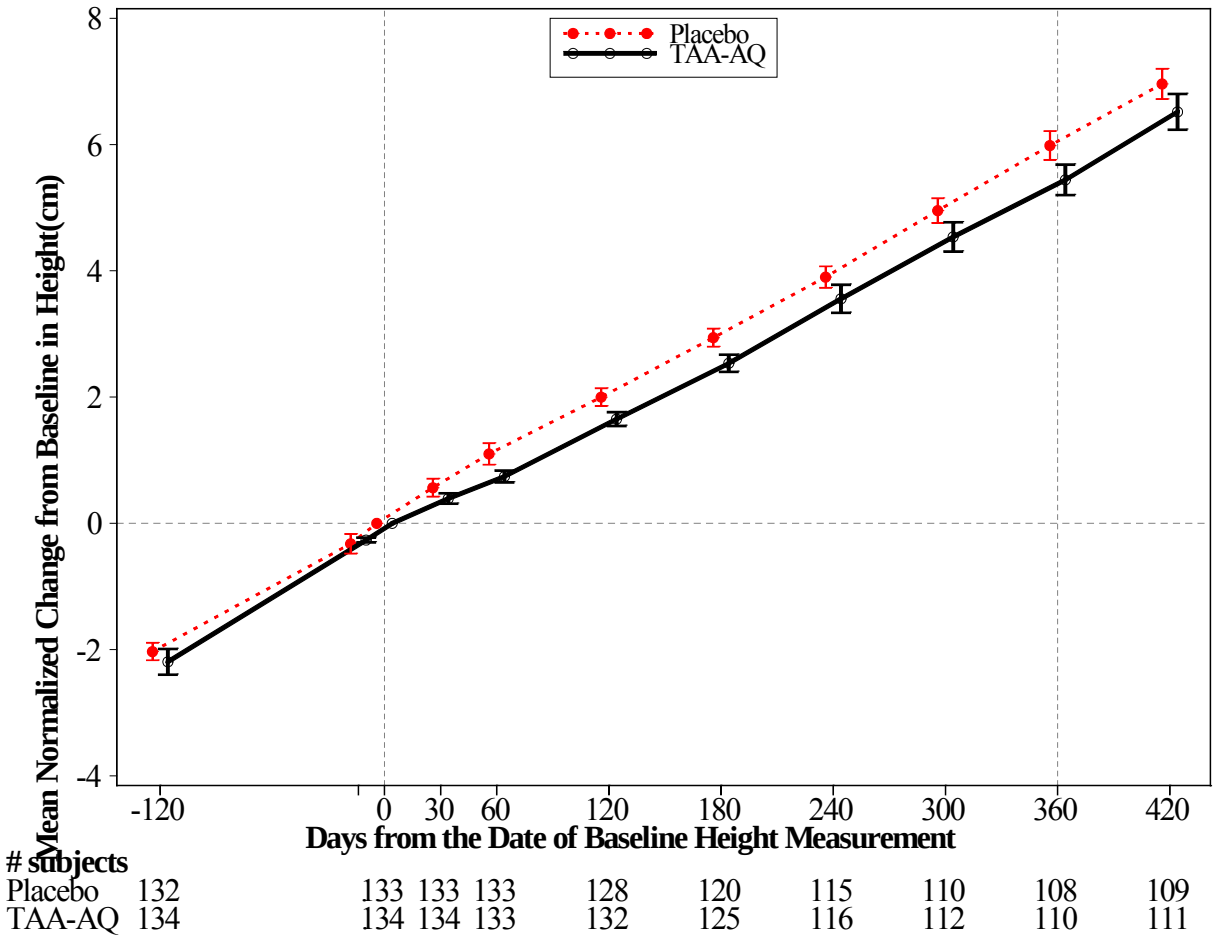
Table includes subjects from Studies RG5029Y-305 (DB, age<12 years), RG5029Y-312 (age<12 years), RG5029Y-314 (age<12 years), XRG5029C/3502 (DB), TRICA_L_04286, and XRG5029C/3503.
PGM=DEVOPS/XRG5029/OTCNDA/ISS2012_02/REPORT/PGM/aepct1_adcom.sas OUT=REPORT/OUTPUT/ae_pt_teae_plac_ped_1pct_t_x.rtf (20MAR2013 - 16:25)

Figure 1 - Serum cortisol geometric mean at the end of treatment by treatment arm - per protocol population



Note: The error bars represent 95% confidence intervals.
PGM=DEVOPS/XRG5029/TRICAL04286/CSR/EXPLO/PGM/pd_sclevelcon_p_EOT_g.sas OUT=EXPLO/OUTPUT/pd_sclevelcon_p__EOT_g_i.rtf (12JUN2013 - 21:27)

Figure 2 - Mean normalized change from baseline in height at each visit – mITT population



mITT population: All randomized and treated subjects with at least 3 post-randomization height measurements during double-blind treatment period, excluding those from GCP noncompliant sites.
Normalized change from baseline at a visit was calculated as (Change from baseline)x(Nominal day interval) /abs(Actual day interval between 2 height measurements).
The nominal day intervals are -120, -14, 0, 30, 60, 120, 180, 240, 300, 360, and 420 days for Visits 1 to 11, respectively. The sample sizes on Day -14 were as same as those at baseline.
The two long vertical lines represent the start and end of study treatment. The short vertical lines represent 95% confidence intervals for the means.
PGM=PRODOPS/XRG5029/UMA03503/CSR/REPORT/PGM/pd_heightchgplot_m_g.sas OUT=REPORT/OUTPUT/pd_heightchgplot_m_g_i.rtf (13JAN2012 - 14:21)

APPENDIX 6: SERIOUS ADVERSE EVENTS IN CLINICAL STUDIES

Study	Treatment	Patient ID	Age(yr), Gender (M/F)	Description of Event, Hospitalized (Yes/No)[a]	Treatment Emergent, Duration (days)	Treatment Related (Yes/No)	Outcome, AE leading to treatment discontinuation (Yes/No)
All controlled studies in adult/adolescent subjects							
301	Placebo	84000150104	23, M	Road traffic accident, Yes	TEAE, 10	No	Recovered without sequelae, Yes
303	TAA-AQ 220 mcg	05601343131	22, M	Skull fracture, No	TEAE, Unknown	No	Recovered without sequelae, No
		25002651103	43, F	Appendicitis, No	Post-treatment, 5	No	Recovered without sequelae, No
	Other-Beconase	05601353111	63, M	Facial paresis, No	Post-treatment, 23	No	Recovered without sequelae, No
309	TAA-AQ 220/110 mcg	84005210241	45, F	Skull fracture, No	TEAE, 60	No	Recovered without sequelae, Yes
4007	Other-Budesonide(Rhinocort)	84000190016	13, M	Limb injury, Yes	TEAE. 5	No	Recovered without sequelae, No
435	Other-Flonase	84000010003	28, F	Overdose, Yes	TEAE, 2	No	Recovered without sequelae, No
				Depression, Yes	TEAE, 5	No	Recovered without sequelae, No
40004 [a]	TAA-AQ 220 mcg	47501	47, F	Asthma, No	TEAE, Unknown	No	Unknown, Unknown

Study	Treatment	Patient ID	Age(yr), Gender (M/F)	Description of Event, Hospitalized (Yes/No)[a]	Treatment Emergent, Duration (days)	Treatment Related (Yes/No)	Outcome, AE leading to treatment discontinuation (Yes/No)
All controlled studies in pediatric subjects							
314	TAA-AQ 220 mcg	84001860056	6, M	Croup infectious, Yes	TEAE, 5	No	Recovered without sequelae, Yes
				Pyrexia, Yes	TEAE, 5	No	Recovered without sequelae, Yes
315 [a]	Placebo	00043	9, M	Asthma, Yes	TEAE, 2	No	Recovered without sequelae; Yes
		00055	6, F	Injury, No	TEAE, 3	No	Recovered without sequelae; No
	TAA-AQ 110 mcg	00019	8, M	Suicidal ideation, Yes	TEAE, 6	No	Recovered without sequelae; No
3502DB	Placebo	84000700005	2, M	Bronchitis, Yes	Pre-treatment, 3	No	Recovered without sequelae, No
4286	Placebo	84000080002	10, M	Humerus fracture, No	TEAE, 71	No	Recovered without sequelae, No
All long-term studies in adult/adolescent subjects							
305LT	TAA-AQ 220/110 mcg	84000160206	37, F	Meningioma, No	Post-treatment, 11	No	Recovered without sequelae, Yes
				Papilloedema, No	TEAE, 81	No	Recovered with sequelae, Yes

Study	Treatment	Patient ID	Age(yr), Gender (M/F)	Description of Event, Hospitalized (Yes/No)[a]	Treatment Emergent, Duration (days)	Treatment Related (Yes/No)	Outcome, AE leading to treatment discontinuation (Yes/No)
		84006690120	33, M	Cerebral haemorrhage, Yes	TEAE, 13	No	Recovered without sequelae, No
		84006690135	27, M	Testis cancer, No	TEAE, Ongoing	No	Ongoing, Yes
		84006700082	49, F	Omental infarction, Yes	TEAE, 5	No	Recovered without sequelae, No
901	TAA-AQ 220 mcg	25000030178	23, F	Sinusitis, Yes	TEAE, 7	No	Recovered without sequelae, No
		25005680113	24, M	Ligament sprain, Yes	TEAE, 62	No	Recovered without sequelae, No
All long-term studies in pediatric subjects							
3502LT	TAA-AQ 110 mcg	84000110011	3, M	Asthma, Yes	TEAE, 3	No	Recovered without sequelae, Yes
		84000280010	3, M	Appendicitis, Yes	TEAE, 4	No	Recovered without sequelae, Yes
		84000340022	4, M	Adenoidal hypertrophy, Yes	TEAE, 50	No	Recovered without sequelae, No
				Tonsillar hypertrophy, Yes	TEAE, 57	No	Recovered without sequelae, No
		84000350009	3, M	Foreign body, Yes	TEAE, 2	No	Recovered without sequelae, No

Study	Treatment	Patient ID	Age(yr), Gender (M/F)	Description of Event, Hospitalized (Yes/No)[a]	Treatment Emergent, Duration (days)	Treatment Related (Yes/No)	Outcome, AE leading to treatment discontinuation (Yes/No)
		84000380021	4, F	Lymphadenitis, Yes	TEAE, 3	No	Recovered without sequelae, No
		84000380051	2, M	Diabetic ketoacidosis, Yes	TEAE, 3	No	Recovered with sequelae, No
		84000440004	3, F	Meningitis aseptic, Yes	TEAE, 3	No	Recovered without sequelae, No
3503	TAA-AQ 110 mcg	84000610011	7, F	Colitis ulcerative, Yes	TEAE, 16	No	Recovered without sequelae, No
		84000660001	4, F	Animal bite, Yes	TEAE, 3	No	Recovered without sequelae, No
Other (short-term non-controlled or non-AR) studies							
4005[a]	TAA-AQ 220 mcg	44-06	48, F	Bronchitis, No	TEAE, Ongoing	No	Ongoing, No
		160-04	55, F	Coronary artery disease, No	TEAE, 2	No	Recovered without sequelae; No

[a] The study database was not available, and the information was based on patient narratives. Adverse events were coded by MedDRA version 14.1